Supporting Information

Discovery and Optimization of Highly Potent and Selective AT_2R Antagonists to Relieve Peripheral Neuropathic Pain

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1. Computational Methods

All the computational procedure was performed in MOE (Chemical Computing Group ULC). The molecular docking simulations of **EMA401** and compound **15** were carried out with the crystal structure of AT2R protein with ligand (PDB: 5UNF). The resulting coordinates were attached in the suporting information as PDB format. The overlay of EMA401 and compound 15 was presented in the Figure S1.

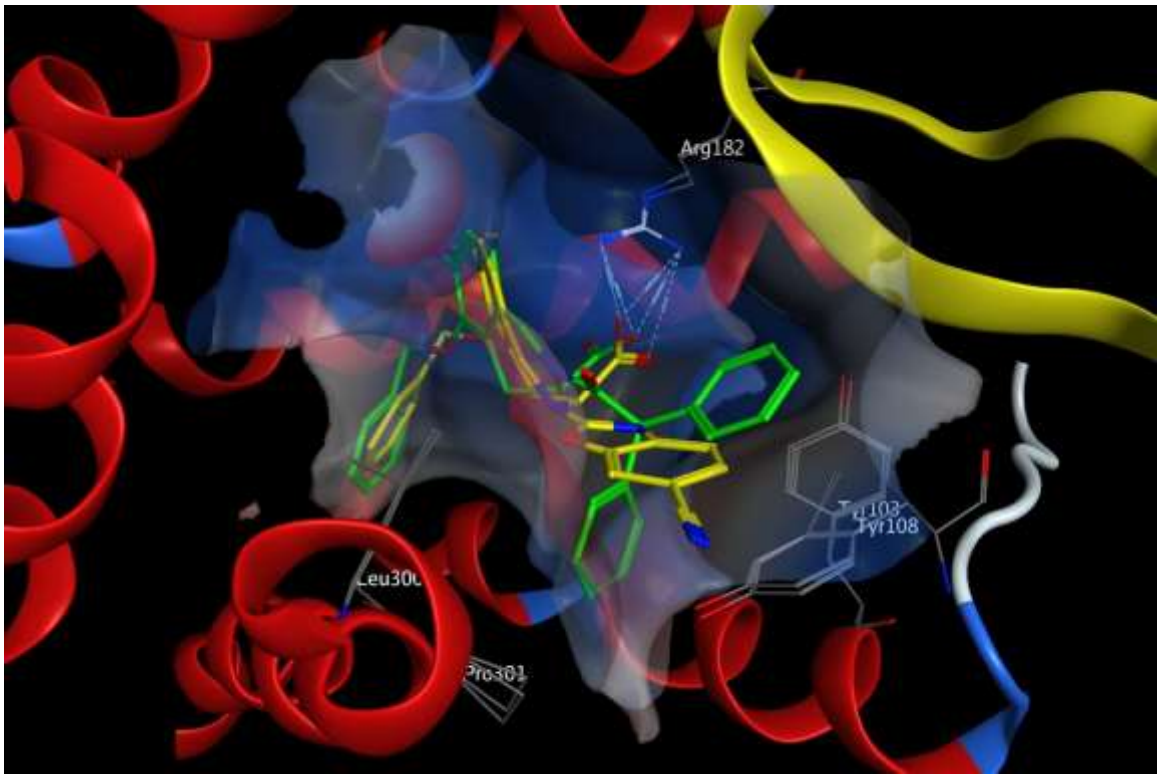


Figure S1. Docking model of **EMA401** and coumpound **15** binding to AT_2R (PDB, 5UNF). AT_2R in ribbons with interaction surface colored by electrostatics, some key residues shown in sticks with carbon in grey, **EMA401** in sticks with carbon in green, and compound **15** in sticks with carbon in yelow.

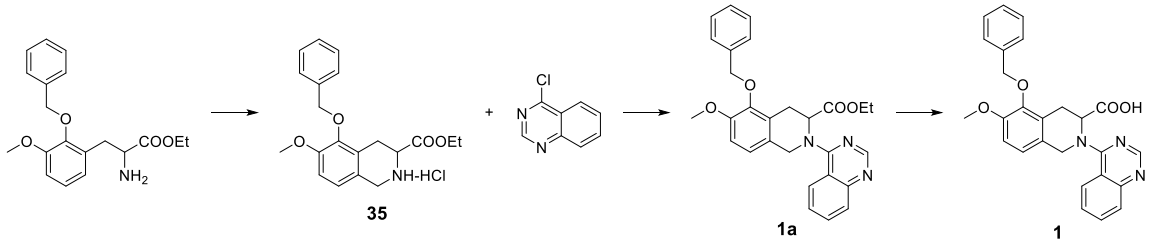
2. Chemistry General Information

EMA401 was prepared according to the reference[1] (purity > 99%, chiral HPLC: retension time, 24.10 min, ee > 99% (chromatographic column: ChiralPak AD-H, 250 × 4.6 mm, 5 μm; T = 25 ℃; λ = 220 nM; mobile phase: Hexane/^{i}PrOH/TFA = 70/30/0.1 (V/V/V); F = 0.4 mL/min; retension time for enantiomers, 20.64 min, 24.40 min)). Preparative HPLC purifications were applied on Gilson GX-281 instrument with C18 reverse phase preparative HPLC columns (Kromasil EternityXT-5-C18, 21.1 x 250 mm; or Waters SunFire Prep C18, 5μm, 19 x 250 mm) eluting with acetonitrile/water (0.1% TFA or NH_4OH). For NMR measurement, Chemical shifts (δ) are reported in parts per million (ppm) relative to TMS (δ = 0.00 ppm) and coupling constant (*J*) are reported in Hertz (Hz). Splitting patterns are indicated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; brs, broad singlet; dd, doublet of doublets. Mass spectrometric identification of compounds was typically conducted using an electrospray ionization

method with an Agilent model 1200 LC/MSD instrument. High resolution mass spectrometric was recorded on an Agilent 6540 UHD Accurate-Mass Q-TOF LC/MS instrument. Specific rotation was recorded on an Autopol automatic polarimeter of Rudolph Research Analytical.

3. Synthetic Procedures and Analytic Data for Key Compounds

5-(Benzyloxy)-6-methoxy-2-(quinazolin-4-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (1)



35 1a 1

Step 1

Ethyl 2-amino-3-(2-(benzyloxy)-3-methoxyphenyl) propanoate **35**[2] (20.5 g, 62.2 mmol) was dissolved in aqueous HCl solution (2N, 250 mL), and formaldehyde in aqueous solution (37%, 50 mL) and THF (5 mL) were added. The mixture was stirred at room temperature overnight. Acetonitrile was added and organic volatiles were concentrated under reduced pressure. The precipitate was filtered and dried to provide ethyl 5-(benzyloxy)-6-methoxy-1,2,3,4- tetrahydroisoquinoline-3-carboxylate hydrochloride as white solid (21.0 g, 91%).

MS *m*/*z* (ESI): calcd for $C_{20}H_{24}NO_4$ $[M+H]^+$, 342.2; found, 342.0.

Step 2

Ethyl 5-(benzyloxy)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate hydrochloride (377 mg, 1.00 mmol), 4-chloroquinazoline (181 mg, 1.10 mmol) and DIPEA (0.55 mL, 3.0 mmol) were dissolved in NMP (7 mL). The reaction was heated to 80℃ for 3 hours. EtOAc (10 mL) was added and washed with water (15 mL) and saturated aqueous NaCl (15 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel chromatography to provide ethyl 5-(benzyloxy)-6-methoxy-2-(quinazolin-4-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (140 mg, 30%).

MS *m*/*z* (ESI): calcd for $C_{28}H_{28}N_3O_4$ $[M+H]^+$, 470.2; found, 470.0.

Step 3

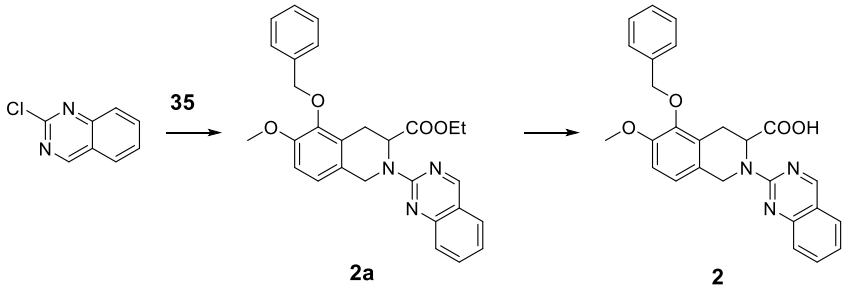
Ethyl 5-(benzyloxy)-6-methoxy-2-(quinazolin-4-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (140 mg, 0.30 mmol) was dissolved in tetrahydrofuran/methanol (6 mL, volume: 2/1). Sodium hydroxide solution (1N, 1.5 mL) was added dropwise. The reaction was stirred at room temperature for 4 hours. The mixture was concentrated under reduced pressure. Water (8 mL) was added and then neutralized with 1N HCl. The precipitate was filtered and washed with water. The filter cake was dried to provide 5-(benzyloxy)-6-methoxy-2-(quinazolin-4-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (100 mg, 76%).

MS *m*/*z* (ESI): calcd for $C_{26}H_{24}N_3O_4$ $[M+H]^+$, 442.2; found, 442.0.

HPLC: Purity 94.6%.

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.77 (s, 1H), 8.59 (s, 1H), 8.23 (d, *J* = 8.0 Hz, 1H), 7.87-7.81 (m, 2H), 7.59 (t, *J* = 7.6 Hz, 1H), 7.51-7.35 (m, 5H), 7.01 (d, *J* = 8.4 Hz, 1H), 6.96 (d, *J* = 8.0 Hz, 1H), 5.29 (t, *J* = 4.8 Hz, 1H), 5.07- 4.89 (m, 4H), 3.83 (s, 3H), 3.42 (dd, *J* = 16.0, 4.4 Hz, 1H), 3.20 (dd, *J* = 16.4, 5.2 Hz, 1H).

5-(Benzyloxy)-6-methoxy-2-(quinazolin-2-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (2)



Step 1

Ethyl 5-(benzyloxy)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate hydrochloride (377 mg, 1.00 mmol), 2-chloroquinazoline (181 mg, 1.10 mmol) and DIPEA (0.55 mL, 3.0 mmol) were dissolved in NMP (7 mL). The reaction was heated to 100℃ for 7 hours. EtOAc (10 mL) was added and washed with water (15 mL) and saturated aqueous NaCl (15 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel chromatography to provide ethyl 5-(benzyloxy)-6-methoxy-2-(quinazolin-2-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (46.0 mg, 10%).

MS *m*/*z* (ESI): calcd for $C_{28}H_{28}N_3O_4$ $[M+H]^+$, 470.2; found, 470.0.

Step 2

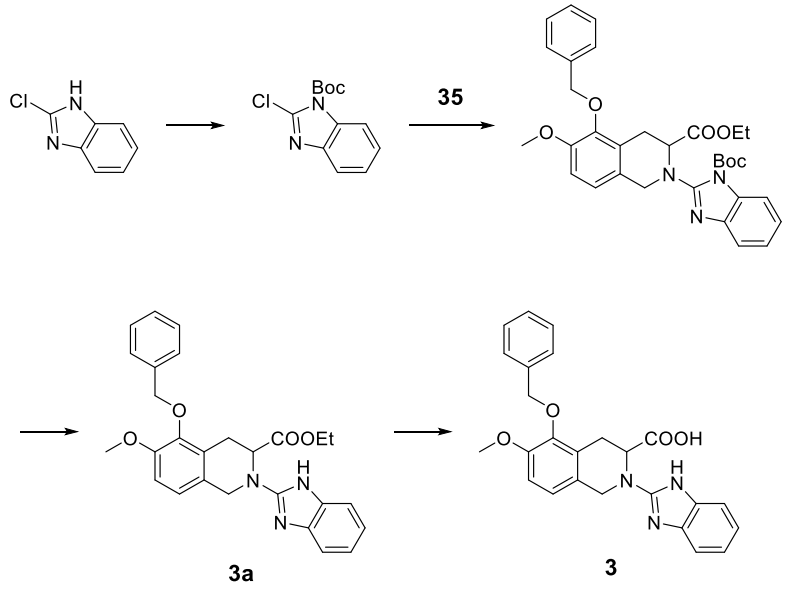
Prepared analogously to **1** using ethyl 5-(benzyloxy)-6-methoxy-2-(quinazolin-2-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate **2a** (46 mg, 0.098 mmol) to provide 5-(benzyloxy)-6-methoxy-2-(quinazolin-2-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (25 mg, 58%).

MS *m*/*z* (ESI): calcd for $C_{26}H_{24}N_3O_4$ $[M+H]^+$, 442.2; found, 442.0.

HPLC: Purity > 99%.

^{1}H NMR (400 MHz, d_6-DMSO) δ 9.18 (s, 0.4 H), 9.13 (s, 0.6 H), 7.79 (d, *J* = 7.2 Hz, 1 H), 7.69 (t, *J* = 7.2 Hz, 1 H), 7.53- 7.32 (m, 7 H), 7.21 (t, *J* = 6.2 Hz, 1 H), 6.98- 6.89 (m, 2 H), 5.51 (d, *J* = 5.2 Hz, 1 H), 5.26 (d, *J* = 16.4 Hz, 0.4 H), 5.07 (d, *J* = 16.8 Hz, 0.6 H), 4.90 (s, 2 H), 4.66 (t, *J* = 18.0 Hz, 1 H), 3.80 (s, 3 H), 3.75 (d, *J* = 16.0 Hz, 1 H), 2.67 (dd, *J* = 16.2, 6.6 Hz, 1 H).

2-(1H-benzo[d]imidazol-2-yl)-5-(benzyloxy)-6-methoxy-1,2,3,4-tetrahydroiso-quinoline-3-carboxylic acid (3)



Step 1

To a solution of 2-chloro-1H-benzo[d]imidazole (1.52 g, 9.96 mmol) in acetonitrile (45 mL) cooled at 0℃ was added Di-tert-butyl dicarbonate (2.40 g, 11.0 mmol) followed by DMAP (122 mg, 1.00 mmol). The mixture was stirred at room temperature for 3 hours. The reaction was then quenched with 50 mL of water and concentrated under reduced pressure. The precipitate was filtered and washed with water. The filter cake was dissolved in EtOAc (120 mL) and washed with water (50 mL) and saturated aqueous

NaCl (50 mL), dried over Na_2SO_4, filtered and concentrated to provide tert-butyl 2-chloro-1H-benzo[d]imidazole-1-carboxylate as white solid (2.50 g, 99%).
MS *m*/*z* (ESI): calcd for $C_8H_6ClN_2O_2$ $[M-C_4H_7]^+$, 197.01; found, 196.9.

Step 2

Ethyl 5-(benzyloxy)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate hydrochloride (863 mg, 2.29 mmol) was dissolved in acetonitrile (22 mL). tert-butyl 2-chloro-1H-benzo[d]imidazole-1-carboxylate (686 mg, 2.71 mmol) and DIPEA (1.12 mL, 6.43 mmol) were added. The mixture was then heated at reflux. After 8 hours, the mixture was cooled and concentrated in vacuo. The residue was purified by silica gel chromatography to provide ethyl 5-(benzyloxy)-2-(1-(tert-butoxycarbonyl)-1H-benzo[d]imidazol-2-yl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate as foamed solid (470 mg, 37%).
MS *m*/*z* (ESI): calcd for $C_{32}H_{36}N_3O_6$ $[M+H]^+$, 558.3; found, 557.9.

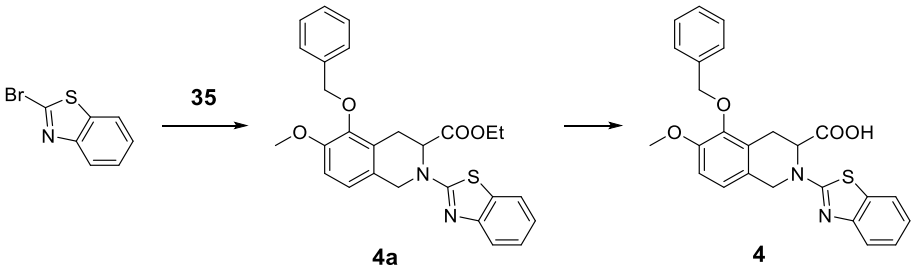
Step 3

Ethyl 5-(benzyloxy)-2-(1-(tert-butoxycarbonyl)-1H-benzo[d]imidazol-2-yl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (470 mg, 0.843 mmol) was added to a solution of trifluoroacetic acid (1 mL) in dichloromethane (2 mL) at 0°C. The reaction was then warmed to room temperature and stirred for 3 hours. The mixture was concentrated in vacuo. Dichloromethane (30 mL) was added and washed with saturated $NaHCO_3$ (20 mL) and saturated aqueous NaCl (20 mL), dried over Na_2SO_4, filtered and concentrated. The resulting material was purified by silica gel chromatography to provide ethyl
2-(1H-benzo[d]imidazol-2-yl)-5-(benzyloxy)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (350 mg, 91%).
MS *m*/*z* (ESI): calcd for $C_{27}H_{28}N_3O_4$ $[M+H]^+$, 458.2; found, 457.9.

Step 4

Prepared analogously to **1** using Ethyl 2-(1H-benzo[d]imidazol-2-yl)-5-(benzyloxy)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate **3a** (60 mg, 0.13 mmol) to provide 2-(1H-benzo[d]imidazol-2-yl)-5-(benzyloxy)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (20 mg, 36%).
MS *m*/*z* (ESI): calcd for $C_{25}H_{24}N_3O_4$ $[M+H]^+$, 430.2; found, 429.9.
HPLC: Purity 91.4%.

2-(Benzo[d]thiazol-2-yl)-5-(benzyloxy)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (4)



Step 1

Ethyl 5-(benzyloxy)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate hydrochloride (50 mg, 0.13 mmol), 2-bromobenzo[d]thiazole (28 mg, 0.13 mmol) and K_2CO_3 (37 mg, 0.26 mmol) were mixed in DMF (1 mL). The reaction was stirred at room temperapture overnight. Water (10 mL) was added and aqueous phase was extracted by EtOAc (5 mL×3). The combined organic phase washed with saturated aqueous NaCl (10 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel chromatography to provide ethyl 2-(benzo[d]thiazol-2-yl)-5-(benzyloxy)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (50 mg, 82%).

MS *m*/*z* (ESI): calcd for $C_{27}H_{27}N_2O_4S$ $[M+H]^+$, 475.2; found, 474.9.

Step 2

Ethyl 2-(benzo[d]thiazol-2-yl)-5-(benzyloxy)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (50 mg, 0.11 mmol) was dissolved tetrahydrofuran (2 mL). The solution of lithium hydroxide monohydrate (9 mg, 0.22 mmol) and water (0.2 mL) was added dropwise. The reaction was stirred at room temperature overnight. The mixture was acidified with 2N HCl and extracted by EtOAc (10 mL×2). The combined organic phase was dried over Na2SO4, filtered and concentrated. The residue was purified by silica gel chromatography to provide 2-(benzo[d]thiazol-2-yl)-5-(benzyloxy)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (15 mg, 30%).

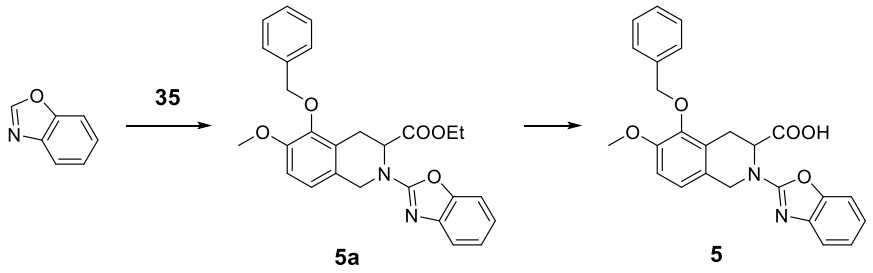
MS *m*/*z* (ESI): calcd for $C_{25}H_{23}N_2O_4S$ $[M+H]^+$, 447.1; found, 446.9.

HPLC: Purity 95.6%.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.84 (d, *J* = 7.6 Hz, 1H), 7.46- 7.31 (m, 7H), 7.14- 7.09 (m, 2H), 7.03 (d, *J* = 8.8 Hz, 1H), 5.19 (s, 1H), 5.00 (d, *J* = 10.8 Hz, 1H), 4.87 (d, *J* = 10.8 Hz, 1H), 4.71 (d, *J* = 15.6 Hz, 1H), 4.64 (d, *J* = 14.8 Hz, 1H), 3.85 (s, 3H), 3.58-3.57 (m, 1H), 3.01 (dd, *J* = 16.6, 6.6 Hz, 1H).

2-(Benzo[d]oxazol-2-yl)-5-(benzyloxy)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-3-

carboxylic acid (5)



Step 1

Ethyl 5-(benzyloxy)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate hydrochloride (754 mg, 2.00 mmol) was dissolved in acetonitrile (10 mL). Benzo[d]oxazole (285 mg, 2.39 mmol), silver carbonate (660 mg, 2.39 mmol), and benzoic acid (448 mg, 3.67 mmol) were added. The reaction was heated at 60℃ for 8 hours. The mixture was filtered and concentrated. The resulting crude was purified by silica gel chromatography to provide ethyl 2-(benzo[d]oxazol-2-yl)-5-(benzyloxy)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carb oxylate (120 mg, 13%).

MS *m*/*z* (ESI): calcd for $C_{27}H_{27}N_2O_5$ $[M+H]^+$, 459.2; found, 458.9.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50- 7.29 (m, 7H), 7.19 (t, *J* = 7.6 Hz, 1H), 7.05 (t, *J* = 7.8 Hz, 1H), 6.94 (d, *J* = 8.4 Hz, 1H), 6.86 (d, *J* = 8.0 Hz, 1H), 5.20 (d, *J* = 3.2 Hz, 1H), 5.05 (d, *J* = 10.4 Hz, 1H), 4.96- 4.91 (m, 2H), 4.80 (d, *J* = 15.6 Hz, 1H), 4.13- 4.00 (m, 2H), 3.87 (s, 3H), 3.65 (d, *J* = 16.4 Hz, 1H), 2.94 (dd, *J* = 16.4, 6.0 Hz, 1H), 1.10 (t, *J* = 7.0 Hz, 3H).

Step 2

Ethyl 2-(benzo[d]oxazol-2-yl)-5-(benzyloxy)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (120 mg, 0.26 mmol) was dissolved in tetrahydrofuran/methanol (5 mL, volume: 3/2). Sodium hydroxide solution (1N, 1.5 mL) was added dropwise. The reaction was stirred at room temperature for 2 hours. The mixture was concentrated under reduced pressure. Water (6 mL) was added and then neutralized with 1N HCl. The precipitate was filtered and washed with water (3 mL). The filter cake was dried to provide 2-(benzo[d]oxazol-2-yl)-5-(benzyloxy)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (90 mg, 81%).

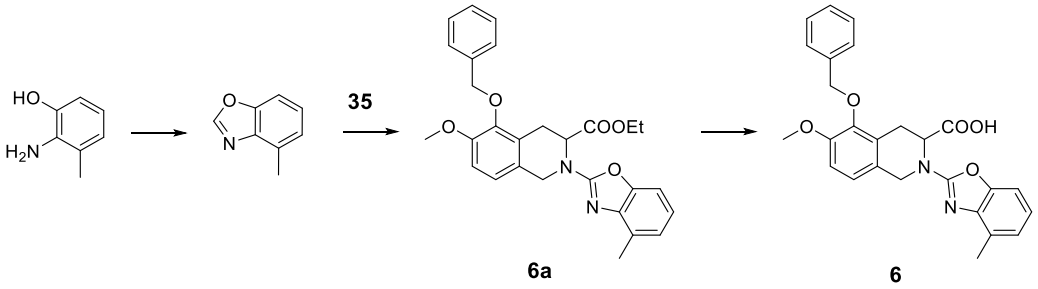
MS *m*/*z* (ESI): calcd for $C_{25}H_{23}N_2O_5$ $[M+H]^+$, 431.2; found, 430.9.

HPLC: Purity 93.2%.

^{1}H NMR (400 MHz, DMSO-d_6) δ 13.05 (s, 1H), 7.49-7.34 (m, 7H), 7.19 (t, *J* = 7.6 Hz, 1H), 7.08-7.00 (m, 3H), 5.11 (d, *J* = 3.6 Hz, 1H), 4.98 (d, *J* = 10.8 Hz, 1H), 4.86 (d, *J* =

10.8 Hz, 1H), 4.80 (d, *J* = 15.6 Hz, 1H), 4.68 (d, *J* = 15.6 Hz, 1H), 3.84 (s, 3H), 3.52 (d, *J* = 16.4 Hz, 1H), 2.99 (dd, *J* = 16.4, 5.8 Hz, 1H).

5-(Benzyloxy)-6-methoxy-2-(4-methylbenzo[d]oxazol-2-yl)-1,2,3,4-tetrahydroiso-quinoline-3-carboxylic acid (6)



Step 1

2-Amino-3-methylphenol (615 mg, 4.99 mmol) was dissolved in triethyl orthoformate (9 mL) and heated to reflux for 4 hours. The mixture was cooled to room temperature and concentrated under reduced pressure. The residue was purified by silica gel chromatography to provide 4-methylbenzo[d]oxazole as red oil (500 mg, 75%).

Step 2

Prepared analogously to **5a** using ethyl 5-(benzyloxy)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate hydrochloride **35** (377 mg, 1.00 mmol) and 4-methylbenzo[d]oxazole (160 mg, 1.20 mmol) to provide ethyl 5-(benzyloxy)-6-methoxy-2-(4-methylbenzo[d]oxazol-2-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (180 mg, 38%).

MS *m*/*z* (ESI): calcd for $C_{28}H_{29}N_2O_5$ $[M+H]^+$, 473.2; found, 473.0.

Step 3

Prepared analogously to **5** using 5-(benzyloxy)-6-methoxy-2-(4-methylbenzo[d]oxazol-2-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate **6a** (180 mg, 0.381 mmol) to provide 5-(benzyloxy)-6-methoxy-2-(4-methylbenzo[d]oxazol-2-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (27 mg, 16%).

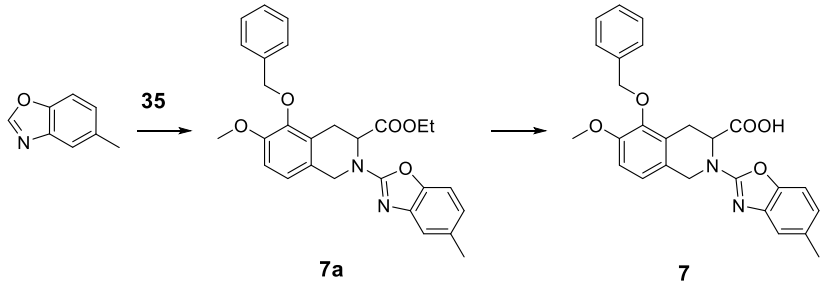
MS *m*/*z* (ESI): calcd for $C_{26}H_{25}N_2O_5$ $[M+H]^+$, 445.2; found, 444.9.

HPLC: Purity 95.8%.

^{1}H NMR (400 MHz, DMSO-d_6) δ 13.05 (s, 1H), 7.49- 7.32 (m, 5H), 7.27 (d, *J* = 8.4 Hz, 1H), 7.09 (d, *J* = 8.4 Hz, 1H), 7.01 (d, *J* = 7.6 Hz, 2H), 6.95 (t, *J* = 8.0 Hz, 1H), 5.13 (d, *J* = 4.0 Hz, 1H), 4.98 (d, *J* = 10.8 Hz, 1H), 4.86 (d, *J* = 10.8 Hz, 1H), 4.80 (d, *J* = 16.0 Hz,

1H), 4.67 (d, *J* = 15.2 Hz, 1H), 3.84 (s, 3H), 3.54 (d, *J* = 16.8 Hz, 1H), 2.98 (dd, *J* = 11.4, 6.4 Hz, 1H), 2.41 (s, 3H).

5-(Benzyloxy)-6-methoxy-2-(5-methylbenzo[d]oxazol-2-yl)-1,2,3,4-tetrahydroiso-quinoline-3-carboxylic acid (7)



Step 1

Prepared analogously to **5a** using ethyl 5-(benzyloxy)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate hydrochloride **35** (377 mg, 1.00 mmol) and 5-methylbenzo[d]oxazole (160 mg, 1.20 mmol to provide ethyl 5-(benzyloxy)-6-methoxy-2-(5-methylbenzo[d]oxazol-2-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (230 mg, 49%).

MS *m*/*z* (ESI): calcd for $C_{28}H_{29}N_2O_5$ $[M+H]^+$, 473.2; found, 473.0.

Step 2

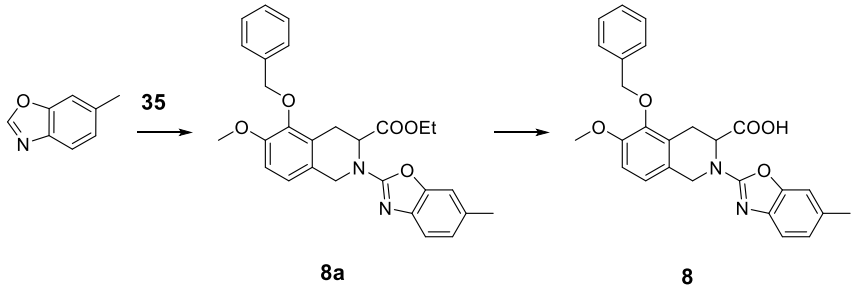
Prepared analogously to **5** using 5-(benzyloxy)-6-methoxy-2-(5-methylbenzo[d]oxazol-2-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate **7a** (230 mg, 0.487 mmol) to provide 5-(benzyloxy)-6-methoxy-2-(5-methylbenzo[d]oxazol-2-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (160 mg, 36%).

MS *m*/*z* (ESI): calcd for $C_{26}H_{25}N_2O_5$ $[M+H]^+$, 445.2; found, 445.0.

HPLC: Purity 97.5%.

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.99 (s, 1H), 7.48-7.31 (m, 6H), 7.15 (s, 1H), 7.06 (d, *J* = 8.8 Hz, 1H), 7.01 (d, *J* = 8.4 Hz, 1H), 6.86 (d, *J* = 8.0 Hz, 1H), 5.09 (d, *J* = 4.4 Hz, 1H), 4.98 (d, *J* = 11.2 Hz, 1H), 4.86 (d, *J* = 11.2 Hz, 1H), 4.78 (d, *J* = 16.0 Hz, 1H), 4.66 (d, *J* = 16.0 Hz, 1H), 3.84 (s, 3H), 3.51 (d, *J* = 16.4 Hz, 1H), 2.99 (dd, *J* = 16.0, 6.4 Hz, 1H), 2.35 (s, 3H).

5-(Benzyloxy)-6-methoxy-2-(6-methylbenzo[d]oxazol-2-yl)-1,2,3,4-tetrahydroiso-quinoline-3-carboxylic acid (8)



Step 1

Prepared analogously to **5a** using ethyl 5-(benzyloxy)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate hydrochloride **35** (377 mg, 1.00 mmol) and 6-methylbenzo[d]oxazole (160 mg, 1.20 mmol) to provide ethyl 5-(benzyloxy)-6-methoxy-2-(6-methylbenzo[d]oxazol-2-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (100 mg, 21%).

MS *m*/*z* (ESI): calcd for $C_{28}H_{29}N_2O_5$ $[M+H]^+$, 473.2; found, 473.0.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 7.2 Hz, 2H), 7.41- 7.31 (m, 4H), 7.12 (s, 1H), 7.02 (d, *J* = 8.0 Hz, 1H), 6.95 (d, *J* = 8.4 Hz, 1H), 6.87 (d, *J* = 8.4 Hz, 1H), 5.18 (d, *J* = 3.2 Hz, 1H), 5.05 (d, *J* = 10.8 Hz, 1H), 4.96- 4.90 (m, 2H), 4.79 (d, *J* = 15.6 Hz, 1H), 4.13- 4.01 (m, 2H), 3.88 (s, 3H), 3.64 (dd, *J* = 16.2, 2.2 Hz, 1H), 2.94 (dd, *J* = 16.4, 6.0 Hz, 1H), 2.41 (s, 3H), 1.11 (t, *J* = 7.2 Hz, 3H).

Step 2

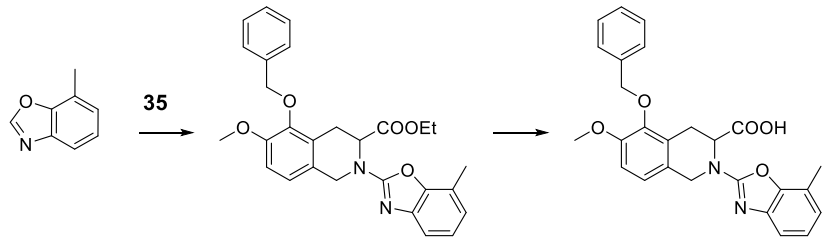
Prepared analogously to **5** using ethyl 5-(benzyloxy)-6-methoxy-2-(6-methylbenzo[d]oxazol-2-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate **8a** (100 mg, 0.212 mmol) to provide 5-(benzyloxy)-6-methoxy-2-(6-methylbenzo[d]oxazol-2-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (50 mg, 54%),

MS *m*/*z* (ESI): calcd for $C_{26}H_{25}N_2O_5$ $[M+H]^+$, 445.2; found, 445.0.

HPLC: Purity 98.1%.

^{1}H NMR (400 MHz, DMSO-d_6) δ 13.00 (s, 1H), 7.49-7.36 (m, 5H), 7.28 (s, 1H), 7.22 (d, *J* = 7.6 Hz, 1H), 7.07-7.00 (m, 3H), 5.08 (d, *J* = 4.8 Hz, 1H), 4.98 (d, *J* = 11.2 Hz, 1H), 4.86 (d, *J* = 11.2 Hz, 1H), 4.78 (d, *J* = 15.2 Hz, 1H), 4.65 (d, *J* = 15.2 Hz, 1H), 3.84 (s, 3H), 3.51 (d, *J* = 16.0 Hz, 1H), 2.98 (dd, *J* = 16.8, 6.8 Hz, 1H), 2.36 (s, 3H).

5-(Benzyloxy)-6-methoxy-2-(7-methylbenzo[d]oxazol-2-yl)-1,2,3,4-tetrahydroiso-quinoline-3-carboxylic acid (9)



9a **9**

Step 1

Prepared analogously to **5a** using ethyl 5-(benzyloxy)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate hydrochloride **35** (377 mg, 1.00 mmol) and 7-methylbenzo[d]oxazole (160 mg, 1.20 mmol) to provide ethyl 5-(benzyloxy)-6-methoxy-2-(7-methylbenzo[d]oxazol-2-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (140 mg, 30%).

MS *m*/*z* (ESI): calcd for $C_{28}H_{29}N_2O_5$ $[M+H]^+$, 473.2; found, 473.0.

Step 2

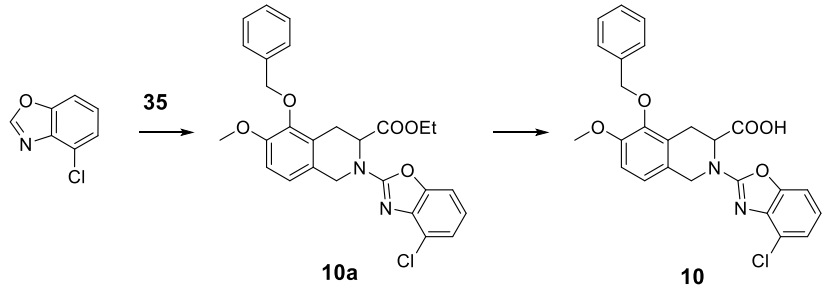
Prepared analogously to **5** using ethyl 5-(benzyloxy)-6-methoxy-2-(7-methylbenzo[d]oxazol-2-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate **9a** (140 mg, 0.296 mmol) to provide 5-(benzyloxy)-6-methoxy-2-(7-methylbenzo[d]oxazol-2-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (110 mg, 83%).

MS *m*/*z* (ESI): calcd for $C_{26}H_{25}N_2O_5$ $[M+H]^+$, 445.2; found, 445.0.

HPLC: Purity 97.1%.

^{1}H NMR (400 MHz, DMSO-d_6) δ 13.04 (s, 1H), 7.52-7.36 (m, 5H), 7.15 (d, *J* = 7.6 Hz, 1H), 7.09-7.00 (m, 3H), 6.88 (d, *J* = 7.2 Hz, 1H), 5.13 (d, *J* = 4.4 Hz, 1H), 4.98 (d, *J* = 10.8 Hz, 1H), 4.86 (d, *J* = 10.4 Hz, 1H), 4.81 (d, *J* = 16.0 Hz, 1H), 4.68 (d, *J* = 15.6 Hz, 1H), 3.84 (s, 3H), 3.53 (d, *J* = 16.4 Hz, 1H), 2.98 (dd, *J* = 16.4, 6.4 Hz, 1H), 2.41 (s, 3H).

5-(Benzyloxy)-2-(4-chlorobenzo[d]oxazol-2-yl)-6-methoxy-1,2,3,4-tetrahydroiso-quinoline-3-carboxylic acid (10)



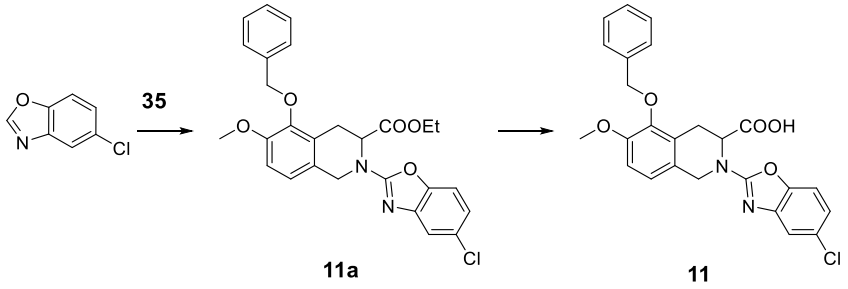
10a **10**

Step 1

Prepared analogously to **5a** using ethyl 5-(benzyloxy)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate hydrochloride **35** (377 mg, 1.00 mmol) and 4-chlorobenzo[d]oxazole (184 mg, 1.20 mmol) to provide ethyl 5-(benzyloxy)-2-(4-chlorobenzo[d]oxazol-2-yl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (30 mg, 30%).
MS *m*/*z* (ESI): calcd for $C_{27}H_{26}ClN_2O_5$ $[M+H]^+$, 493.2; found, 493.0.

Step 2
Prepared analogously to **5** using ethyl 5-(benzyloxy)-2-(4-chlorobenzo[d]oxazol-2-yl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate **10a** (30 mg, 0.06 mmol) to provide
5-(benzyloxy)-2-(4-chlorobenzo[d]oxazol-2-yl)-6-methoxy-1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid (8 mg, 29%).
MS *m*/*z* (ESI): calcd for $C_{25}H_{22}ClN_2O_5$ $[M+H]^+$, 465.1; found, 464.9.
HPLC: Purity 97.2%.

5-(Benzyloxy)-2-(5-chlorobenzo[d]oxazol-2-yl)-6-methoxy-1,2,3,4-tetrahydroiso-quinoline-3-carboxylic acid (11)



Step 1
Prepared analogously to **5a** using ethyl 5-(benzyloxy)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate hydrochloride **35** (377 mg, 1.00 mmol) and 5-chlorobenzo[d]oxazole (184 mg, 1.20 mmol) to provide ethyl 5-(benzyloxy)-2-(5-chlorobenzo[d]oxazol-2-yl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (80 mg, 16%).
MS *m*/*z* (ESI): calcd for $C_{27}H_{26}ClN_2O_5$ $[M+H]^+$, 493.2; found, 492.9.

Step 2
Prepared analogously to **5** using ethyl 5-(benzyloxy)-2-(5-chlorobenzo[d]oxazol-2-yl)-6-methoxy-1,2,3,4-tetrahydroisoquinolin

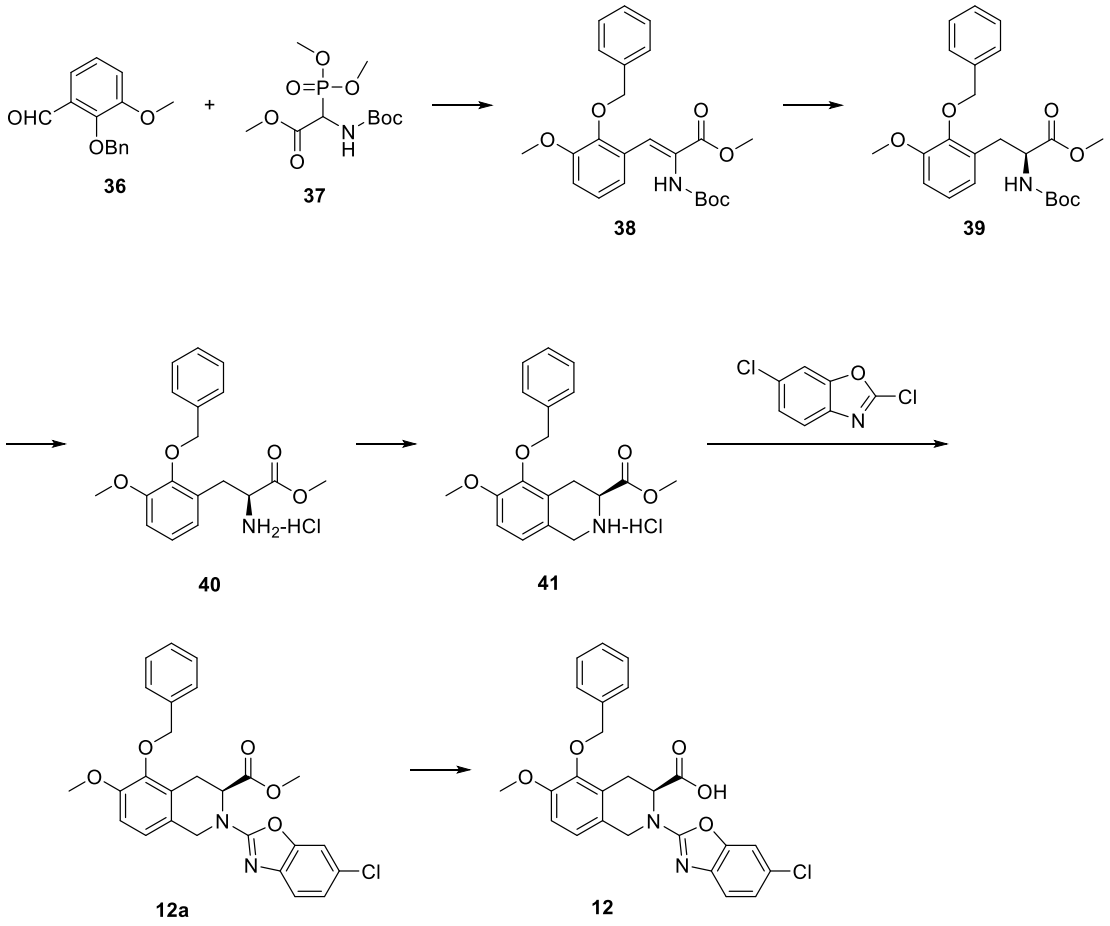
e-3-carboxylate **11a** (80 mg, 0.16 mmol) to provide 5-(benzyloxy)-2-(5-chlorobenzo[d]oxazol-2-yl)-6-methoxy-1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid (60 mg, 81%).

MS *m*/*z* (ESI): calcd for $C_{25}H_{22}ClN_2O_5$ $[M+H]^+$, 465.1; found, 464.9.

HPLC: Purity 97.0%.

^{1}H NMR (400 MHz, DMSO-d_6) δ 13.11 (s, 1H), 7.50-7.34 (m, 7H), 7.10-7.00 (m, 3H), 5.09 (d, *J* = 4.0 Hz, 1H), 4.98 (d, *J* = 10.8 Hz, 1H), 4.85 (d, *J* = 11.2 Hz, 1H), 4.79 (d, *J* = 16.0 Hz, 1H), 4.68 (d, *J* = 16.0 Hz, 1H), 3.84 (s, 3H), 3.53 (d, *J* = 16.0 Hz, 1H), 2.99 (dd, *J* = 15.6, 6.4 Hz, 1H).

(S)-5-(Benzyloxy)-2-(6-chlorobenzo[d]oxazol-2-yl)-6-methoxy-1,2,3,4-tetrahydroiso-quinoline-3-carboxylic acid (12)



Step 1

Methyl 2-((tert-butoxycarbonyl)amino)-2-(dimethoxyphosphoryl)acetate (191 g, 0.643 mol) and 1,1,3,3-Tetramethylguanidine (81.7 g, 0.709 mol) were dissolved in tetrahydrofuran (700 mL) and stirred at 0°C. 2-(Benzyloxy)-3-methoxybenzaldehyde

(136 g, 0.561 mol) in tetrahydrofuran (500 mL) was added and stirred at room temperature overnight. The solution was concentrated under reduced pressure. EtOAc (1000 mL) was added and the organic phase was washed with 1N HCl solution (300 mL×3) and saturated aqueous NaCl (300 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by crystallization with n-Heptane/EtOAc to provide methyl (Z)-3-(2-(benzyloxy)-3-methoxyphenyl)-2-((tert-butoxycarbonyl)amino)acrylate as white solid (205 g, 88 %).

MS *m*/*z* (ESI): calcd for $C_{18}H_{20}NO_4$ $[M-C_5H_7O_2]^+$, 314.1; found, 314.0.

Step 2

Methyl (Z)-3-(2-(benzyloxy)-3-methoxyphenyl)-2-((tert-butoxycarbonyl)amino)acrylate (100 g, 0.242 mol) was dissolved in methanol (1000 mL). (R)-N-Methyl-N-diphenylphosphino-1-[(S)-2-diphenylphosphino)ferrocenyl]ethylamine[3] (2.00 g, CAS No.: 406680-94-2) and bis(1,5-cyclooctadiene)rhodium(I) tetrafluoroborate (2.00 g) was added. The reaction was stirred under 1 atm of hydrogen at room temperature for 2 hours. The solution was concentrated. The residue was added EtOAc (150 mL) and n-Hexane (900 mL). The mixture was filtered. The filtration was concentrated to provide crude methyl (S)-3-(2-(benzyloxy)-3-methoxyphenyl)-2-((tert-butoxycarbonyl)amino)-propanoate as colorless oil (100 g). The NMR sample was purified by silica gel chromatography.

MS *m*/*z* (ESI): calcd for $C_{18}H_{22}NO_4$ $[M-C_5H_7O_2]^+$, 316.2; found, 316.0.

Chiral HPLC: retension time, 25.36 min, ee = 98.7% (chromatographic column: Chiralcel OD-H, 250 × 4.6 mm, 5 μm; T = 25 °C; λ = 275 nM; mobile phase: Hexane/^{i}PrOH/DEA = 95/5/0.1 (V/V/V); F = 1.0 mL/min; retension time for enantiomers, 15.66 min, 25.36 min). The stereochemical configuration of **39** was specified as S according to the reference[3]. Furthermore, we have converted intermediate **39** to **EMA401** and compared to the **EMA401** synthesized according to the reference[1]. They were proved to be consistent in chiral configuration and showed the similar antagonistic activities on hAT_2R.

^{1}H NMR (400 MHz, DMSO- d_6) δ 7.48- 7.32 (m, 5H), 7.23 (d, *J* = 8.0 Hz, 1H), 6.98-6.96 (m, 2H), 6.78 (dd, *J* = 6.4, 2.0 Hz, 1H), 4.96 (q, *J* = 10.4 Hz, 2H), 4.20 (td, *J* = 8.8, 5.2 Hz, 1H), 3.82 (s, 3H), 3.55 (s, 3H), 3.05 (dd, *J* = 13.4, 5.0 Hz, 1H), 2.71 (dd, *J* = 13.2, 10.0 Hz, 1H), 1.30 (s, 9H).

Step 3

Methyl (S)-3-(2-(benzyloxy)-3-methoxyphenyl)-2-((tert-butoxycarbonyl)amino)-propanoate (100 g, 0.241 mol) was dissolved in 1,4-dioxane (200 mL). Solution of hydrogen chloride in 1,4-dioxane (4M, 400 mL) was added and stirred at room temperature for 1 hours. The mixture was added EtOAc (2000 mL) and stirred. The solid was collected and dried to provide methyl (S)-2-amino-3-(2-(benzyloxy)-3-methoxyphenyl)propanoate hydrochloride as white solid (81 g, 96% for two steps). The NMR sample was purified by recrystallization.

MS *m*/*z* (ESI): calcd for $C_{18}H_{22}NO_4$ $[M+H]^+$, 316.2; found, 316.0.

Chiral HPLC: retension time, 10.335 min, ee > 99.0% (chromatographic column: Chiralcel OD-H, 250 × 4.6 mm, 5 μm; T = 25 ℃; λ = 280 nM; mobile phase: Hexane/^{i}PrOH/DEA = 70/30/0.1 (V/V/V); F = 0.8 mL/min; retension time for enantiomers, 10.34 min, 16.09 min).

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.62 (s, 3H), 7.47 -7.32 (m, 5H), 7.03-7.02 (m, 2H), 6.81 – 6.78 (m, 1H), 4.94 (q, *J* = 11.2 Hz, 2H), 4.04 (t, *J* = 7.2 Hz, 1H), 3.83 (s, 3H), 3.50 (s, 2H), 3.05 (d, *J* = 7.2 Hz, 2H).

Step 4

Methyl (S)-2-amino-3-(2-(benzyloxy)-3-methoxyphenyl)propanoate hydrochloride (50.0 g, 0.143 mol) was dissolved in HCl/dioxane (2N, 500 mL). Paraformaldehyde (13.5 g) was added. The mixture was heated to 70 ^{o}C for 1 hour. EtOAc (1500 mL) was added. The solid was collected and dried to rovide methyl (S)-5-(benzyloxy)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate hydrochloride as white solid (42.5g, 82%).

MS *m*/*z* (ESI): calcd for $C_{19}H_{22}NO_4$ $[M+H]^+$, 328.2; found, 328.0.

Chiral HPLC: retension time, 10.43 min, ee = 99.8% (chromatographic column: ChiralPak AD-H, 250 × 4.6 mm, 5 μm; T = 25 ℃; λ = 280 nM; mobile phase: Hexane/^{i}PrOH/DEA = 70/30/0.1 (V/V/V); F = 0.8 mL/min; retension time for enantiomers, 10.43 min, 16.01 min).

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.12 (s, 2H), 7.45 – 7.33 (m, 5H), 7.05 (d, *J* = 8.8 Hz, 1H), 7.00 (d, *J* = 8.4 Hz, 1H), 4.96 (d, *J* = 2.0 Hz, 2H), 4.41 (dd, *J* = 10.8, 5.2 Hz, 1H), 4.22 (q, *J* = 15.6 Hz, 2H), 3.82 (s, 3H), 3.77 (s, 3H), 3.21 (dd, *J* = 17.2, 5.2 Hz, 1H), 2.92 (dd, *J* = 17.6, 11.2 Hz, 1H).

Step 5

Methyl (S)-5-(benzyloxy)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate hydrochloride (80 mg, 0.22 mmol), 2,6-dichlorobenzo[d]oxazole (41 mg, 0.22 mmol) and triethylamine (91 μL, 0.66 mmol) were dissolved in tetrahydrofuran (2 mL). The reaction

was heated to 60℃ for 5 hours. The solution was concentrated under reduced pressure and the residue was purified by silica gel chromatography to provide methyl (S)-5-(benzyloxy)-2-(6-chlorobenzo[d]oxazol-2-yl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (60 mg, 57%).

MS *m*/*z* (ESI): calcd for $C_{26}H_{24}ClN_2O_5$ $[M+H]^+$, 479.1; found, 478.9.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.65 (d, *J* = 1.6 Hz, 1H), 7.48- 7.35 (m, 6H), 7.25 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.07 (d, *J* = 8.4 Hz, 1H), 7.01 (d, *J* = 8.4 Hz, 1H), 5.22 (dd, *J* = 6.0, 2.4 Hz, 1H), 5.00 (d, *J* = 10.8 Hz, 1H), 4.85- 4.79 (m, 2H), 4.67 (d, *J* = 16.0 Hz, 1H), 3.84 (s, 3H), 3.57 (s, 3H), 3.49 (dd, *J* = 16.2, 2.6 Hz, 1H), 3.04 (dd, *J* = 16.2, 6.2 Hz, 1H).

Step 6

Methyl (S)-5-(benzyloxy)-2-(6-chlorobenzo[d]oxazol-2-yl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (60 mg , 0.13 mmol) was dissolved in tetrahydrofuran (2 mL). The solution of lithium hydroxide monohydrate (16 mg, 0.38 mmol) in water (0.2 mL) was added. The reaction was stirred at room temperatue overnight. The solution was acidified with 2N HCl. Water (5 mL) was added and extracted with EtOAc (10 mL×2). The combined organic phase was dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel chromatography to provide

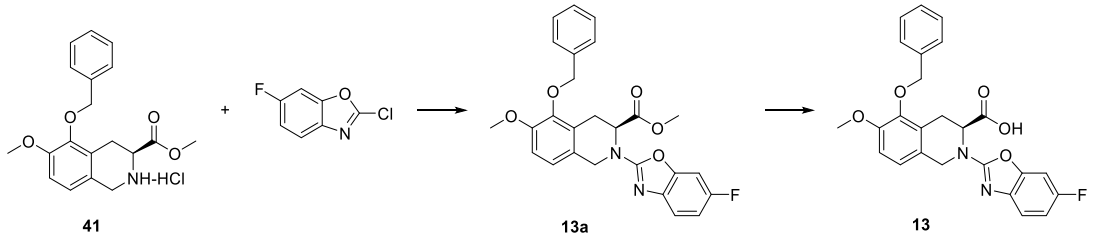
(S)-5-(benzyloxy)-2-(6-chlorobenzo[d]oxazol-2-yl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (30 mg, 52 %).

MS *m*/*z* (ESI): calcd for $C_{25}H_{22}ClN_2O_5$ $[M+H]^+$, 465.1; found, 464.9.

HPLC: Purity > 99%.

^{1}H NMR (400 MHz, DMSO-d_6) δ7.64 (d, *J* = 2.0 Hz, 1H), 7.49-7.34 (m, 6H), 7.24 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.07 (d, *J* = 8.4 Hz, 1H), 7.01 (d, *J* = 8.4 Hz, 1H), 5.10 (dd, *J* = 6.2, 2.2 Hz, 1H), 4.99 (d, *J* = 11.2 Hz, 1H), 4.87 (d, *J* = 11.2 Hz, 1H), 4.79 (d, *J* = 15.6 Hz, 1H), 4.68 (d, *J* = 15.6 Hz, 1H), 3.84 (s, 3H), 3.54 (dd, *J* = 16.2, 1.8 Hz, 1H), 3.00 (dd, *J* = 16.4, 6.4 Hz, 1H).

(S)-5-(Benzyloxy)-2-(6-fluorobenzo[d]oxazol-2-yl)-6-methoxy-1,2,3,4-tetrahydroiso-quinoline-3-carboxylic acid (13)



Step 1

Prepared analogously to **12a** using methyl (S)-5-(benzyloxy)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate hydrochloride **41** (1.2 g, 3.7 mmol) and 2-chloro-6-fluorobenzo[d]oxazole (1.3 g, 7.6 mmol) to provide methyl (S)-5-(benzyloxy)-2-(6-fluorobenzo[d]oxazol-2-yl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (1.3 g, 46%).

MS *m*/*z* (ESI): calcd for $C_{26}H_{24}FN_2O_5$ $[M+H]^+$, 463.2; found, 462.9.

Chiral HPLC: retension time, 15.58 min, ee = 98.9% (chromatographic column: ChiralPak AD-H, 250 × 4.6 mm, 5 μm; T = 25 ℃; λ = 254 nM; mobile phase: Hexane/^{i}PrOH/DEA = 70/30/0.1 (V/V/V); F = 0.8 mL/min; retension time for enantiomers, 15.58 min, 30.80 min).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49-7.29 (m, 6H), 7.06 (dd, *J* = 7.8, 2.2 Hz, 1H), 6.96-6.86 (m, 3H), 5.19 (dd, *J* = 6.4, 2.4 Hz, 1H), 5.05 (d, *J* = 10.8 Hz, 1H), 4.95 (d, *J* = 11.2 Hz, 1H), 4.90 (d, *J* = 15.6 Hz, 1H), 4.76 (d, *J* = 15.2 Hz, 1H), 3.89 (s, 3H), 3.66-3.61 (m, 4H), 2.94 (dd, *J* = 16.4, 6.4 Hz, 1H).

Step 2

Methyl (S)-5-(benzyloxy)-2-(6-fluorobenzo[d]oxazol-2-yl)-6-methoxy-1,2,3,4-tetra-hydroisoquinoline-3-carboxylate (1.3 g, 2.8 mmol) was dissolved in tetrahydrofuran (10 mL) and isopropanol (10 mL). The mixture of calcium chloride (4.8 g, 43 mmol) and sodium hydroxide (0.56 g, 14 mmol) in water (300 mL) was added. The reaction was stirred at room temperature overnight. The reaction was acidified with 1N HCl to adjust pH to about 3. The solution was concentrated. The precipitation was collected, washed with water and dried. The solid was purified by recrystallization with acetone to provide (S)-5-(benzyloxy)-2-(6-fluorobenzo[d]oxazol-2-yl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid as white solid (0.45 g, 45% yield).

MS *m*/*z* (ESI): calcd for $C_{25}H_{22}FN_2O_5$ $[M+H]^+$, 449.2; found, 448.9.

HRMS *m*/*z* (ESI): calcd for $C_{25}H_{22}FN_2O_5$ $[M+H]^+$, 449.1513; found, 449.1514

HPLC: Purity > 99%.

Chiral HPLC: retension time, 29.12 min, ee = 99.0% (chromatographic column: ChiralPak AS-H, 250 × 4.6 mm, 5 μm; T = 25 ℃; λ = 240 nM; mobile phase:

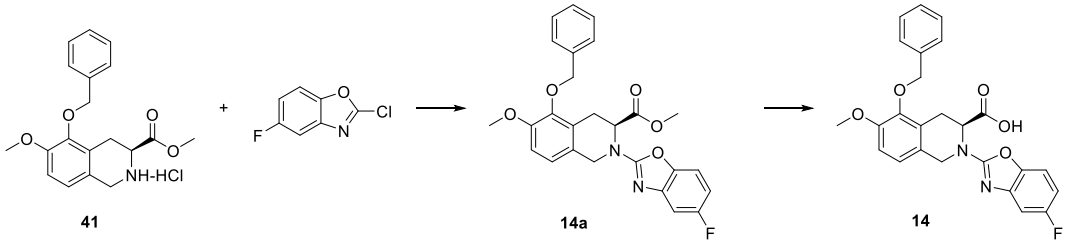
Hexane/^{i}PrOH/DEA = 90/10/0.1 (V/V/V); F = 1.0 mL/min; retension time for enantiomers, 20.48 min, 29.12 min).

$[\alpha]_D^{20}$ + 46.4 (*c* 1.00, MeOH).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.51-7.33 (m, 7H), 7.09-7.01 (m, 3H), 5.09 (dd, *J* = 6.2, 2.6 Hz, 1H), 4.99 (d, *J* = 10.8 Hz, 1H), 4.87 (d, *J* = 11.2 Hz, 1H), 4.78 (d, *J* = 16.0 Hz, 1H), 4.67 (d, *J* = 16.0 Hz, 1H), 3.85 (s, 3H), 3.53 (dd, *J* = 16.2, 2.2 Hz, 1H), 3.00 (dd, *J* = 16.4, 6.4 Hz, 1H).

^{13}C NMR (100 MHz, DMSO-d_6) δ 172.38, 162.69, 157.64 (d, *J* = 234.9 Hz), 151.45, 148.58 (d, *J* = 14.7 Hz), 144.97, 139.59, 137.97, 128.84, 128.66, 128.46, 126.34, 125.03, 122.48, 116.42 (d, *J* = 9.5 Hz), 112.13, 111.33 (d, *J* = 23.4 Hz), 98.56 (d, *J* = 28.8 Hz), 74.53, 56.35, 54.38, 45.18, 25.37.

(S)-5-(Benzyloxy)-2-(5-fluorobenzo[d]oxazol-2-yl)-6-methoxy-1,2,3,4-tetrahydroiso-quinoline-3-carboxylic acid (14)



Step 1

Prepared analogously to **12a** using methyl (S)-5-(benzyloxy)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate hydrochloride **41** (50.0 mg, 0.137 mmol) and 2-chloro-5-fluorobenzo[d]oxazole (23.6 mg, 0.137 mmol) to provide methyl (S)-5-(benzyloxy)-2-(5-fluorobenzo[d]oxazol-2-yl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate as crude without purification (63.0 mg).

MS *m*/*z* (ESI): calcd for $C_{26}H_{24}FN_2O_5$ $[M+H]^+$, 463.2; found, 462.9.

Step 2

Prepared analogously to **12** using (S)-5-(benzyloxy)-2-(5-fluorobenzo[d]oxazol-2-yl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate **14a** (63.0 mg, 0.137 mmol) to provide (S)-5-(benzyloxy)-2-(5-fluorobenzo[d]oxazol-2-yl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (20 mg, 33% for two steps).

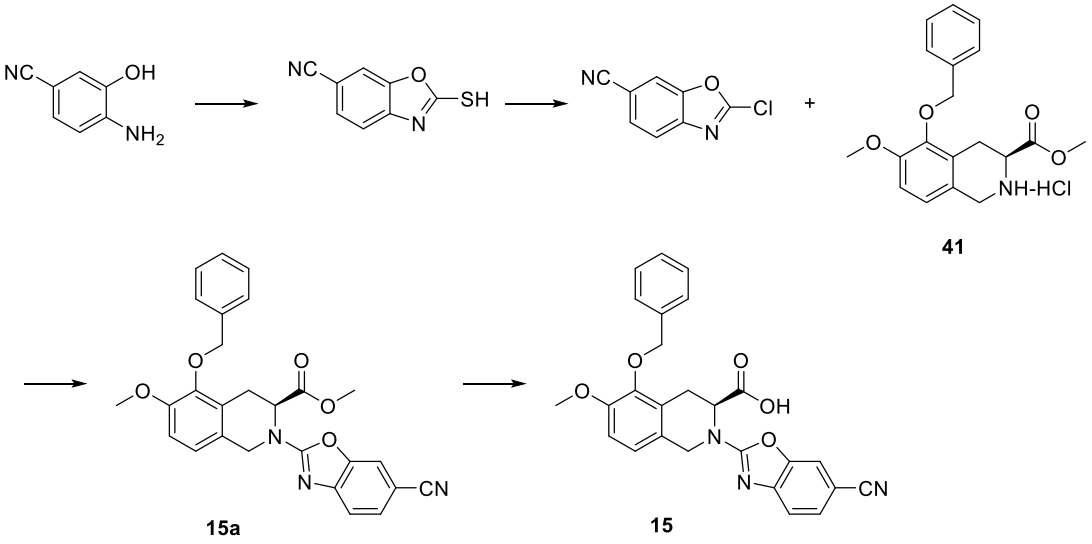
MS *m*/*z* (ESI): calcd for $C_{25}H_{22}FN_2O_5$ $[M+H]^+$, 449.2; found, 448.9.

HPLC: Purity 98.7%.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.50- 7.35 (m, 6H), 7.21 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.08 (d, *J* = 8.6 Hz, 1H), 7.02 (d, *J* = 8.6 Hz, 1H), 6.88 (td, *J* = 9.2, 2.3 Hz, 1H), 5.11 (dd, *J* =

6.2, 2.6 Hz, 1H), 4.99 (d, *J* = 10.8 Hz, 1H), 4.87 (d, *J* = 10.8 Hz, 1H), 4.80 (d, *J* = 15.6 Hz, 1H), 4.69 (d, *J* = 16.0 Hz, 1H), 3.85 (s, 3H), 3.53 (dd, *J* = 16.4, 2.4 Hz, 1H), 3.01 (dd, *J* = 16.0, 6.4 Hz, 1H).

(S)-5-(Benzyloxy)-2-(6-cyanobenzo[d]oxazol-2-yl)-6-methoxy-1,2,3,4-tetrahydroiso-quinoline-3-carboxylic acid (15)



Step 1

4-Amino-3-hydroxybenzonitrile (50 g, 0.37 mol) and potassium ethylxanthate (119 g, 0.742 mol) were dissolved in ethanol (300 mL). The reaction was heated to reflux for 4 hours. The mixture was cooled to room temperature and poured into ice water (500 mL). The mixture was acidified to pH 3 with 2N HCl. The precipitate was collected and dried to provide 2-mercaptobenzo[d]oxazole-6-carbonitrile as brown solid (60 g, 92%).
MS *m*/*z* (ESI): calcd for $C_8H_5N_2OS$ $[M+H]^+$, 177.0; found, 176.8.

Step 2

2-Mercaptobenzo[d]oxazole-6-carbonitrile (50 g, 0.28 mol) was dissolved in thionyl chloride (250 mL). DMF (2.0 mL) was added dropwise. The reaction was heated to reflux for 6 hours. The solution was concentrated under reduced pressure. Petroleum ether (200 mL) was added to the residue. The mixture was stirred at room temperature for 2 hours. The precipitate was filtered and dried to provide 2-chlorobenzo[d]oxazole-6-carbonitrile as white solid (45 g, 90%).
MS *m*/*z* (ESI): calcd for $C_8H_4ClN_2O$ $[M+H]^+$, 179.0; found, 178.7.

Step 3

methyl (S)-5-(benzyloxy)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate hydrochloride **41** (23.0 g, 0.0632 mol) and 2-chlorobenzo[d]oxazole-6-carbonitrile (15.0 g, 0.0840 mol) were dissolved in DMF (100 mL). Potassuim carbonate (14.6 g, 0.106 mol) was added. The reaction was stirred at room temperature for 7 hours. Water (300 mL) was added and extracted with EtOAc (200 mL×2). The combined organic phase was washed with water (100 mL×2) and dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel chromatography to provide methyl (S)-5-(benzyloxy)-2-(6-cyanobenzo[d]oxazol-2-yl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate as white solid (30 g, 91% yield).

MS *m*/*z* (ESI): calcd for $C_{27}H_{24}N_3O_5$ $[M+H]^+$, 470.2; found, 470.0.

HPLC: Purity > 99%. Chiral HPLC: retension time, 27.79 min, ee > 99% (chromatographic column: ChiralPak AD-H, 250 × 4.6 mm, 5 μm; T = 25 ℃; λ = 254 nM; mobile phase: Hexane/^{i}PrOH/DEA = 70/30/0.1 (V/V/V); F = 0.8 mL/min; retension time for enantiomers, 27.79 min, 41.45 min).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 1.2 Hz, 1H), 7.52- 7.46 (m, 3H), 7.42- 7.35 (m, 4H), 6.94 (d, *J* = 8.8 Hz, 1H), 6.88 (d, *J* = 8.4 Hz, 1H), 5.20 (br, 1H), 5.06 (d, *J* = 11.2 Hz, 1H), 4.97- 4.91 (m, 2H), 4.80 (d, *J* = 15.6 Hz, 1H), 3.89 (s, 3H), 3.64 (s, 3H), 3.64 (dd, *J* = 16.2, 3.0 Hz, 1H), 2.95 (dd, *J* = 16.4, 6.4 Hz, 1H).

Step 4

methyl (S)-5-(benzyloxy)-2-(6-cyanobenzo[d]oxazol-2-yl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (10.0 g, 21.3 mmol) was dissolved in tetrahydrofuran (600 mL) and isopropanol (600 mL). The mixture of calcium chloride (35.5 g, 0.320 mol) and sodium hydroxide (4.30 g, 0.107 mol) in water (300 mL) was added. The reaction was stirred at room temperature overnight. The reaction was acidified with 1N HCl to adjust pH to about 3. The solution was concentrated to about 300 mL. The precipitation was collected, washed with water and dried. The solid was purified by recrystallization with acetone to provide (S)-5-(benzyloxy)-2-(6-cyanobenzo[d]oxazol-2-yl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid as white solid (8.8 g, 90% yield).

MS *m*/*z* (ESI): calcd for $C_{26}H_{22}N_3O_5$ $[M+H]^+$, 456.2; found, 455.9.

HRMS *m*/*z* (ESI): calcd for $C_{26}H_{22}N_3O_5$ $[M+H]^+$, 456.1559; found, 456.1558.

HPLC: Purity > 99%.

Chiral HPLC: retension time, 43.31 min, ee = 98.5% (chromatographic column: ChiralPak OD-RH, 150 × 4.6 mm, 5 μm; T = 25 ℃; λ = 300 nM; mobile phase: MeOH/50 mMKPF_6 (adjust pH to 2.0 with H_3PO_4) = 80/20(V/V); F = 0.4 mL/min;

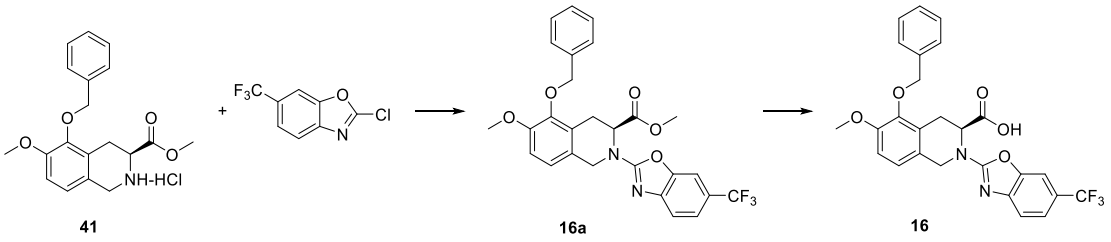
retension time for enantiomers, 43.31 min, 50.45 min).

$[\alpha]_D^{20}$ + 35.7 (*c* 1.00, MeOH).

^{1}H NMR (400 MHz, DMSO-d_6) δ 13.14 (s, 1H), 8.05 (s, 1H), 7.67 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.49-7.34 (m, 6H), 7.09 (d, *J* = 8.4 Hz, 1H), 7.02 (d, *J* = 8.4 Hz, 1H), 5.14 (dd, *J* = 6.0, 2.8 Hz, 1H), 4.98 (d, *J* = 10.8 Hz, 1H), 4.85 (d, *J* = 10.8 Hz, 1H), 4.82 (d, *J* = 15.2 Hz, 1H), 4.73 (d, *J* = 15.2 Hz, 1H), 3.84 (s, 3H), 3.54 (dd, *J* = 16.2, 2.6 Hz, 1H), 3.01 (dd, *J* = 16.4, 5.6 Hz, 1H).

^{13}C NMR (100 MHz, DMSO-d_6) δ 172.01, 164.11, 151.60, 148.29, 147.99, 144.93, 137.94, 130.04, 128.84, 128.67, 128.48, 126.33, 124.75, 122.52, 119.95, 117.05, 113.33, 112.15, 102.46, 74.58, 56.35, 54.72, 44.66, 25.28.

(S)-5-(Benzyloxy)-6-methoxy-2-(6-(trifluoromethyl)benzo[d]oxazol-2-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (16)



41 16a 16

Step 1

Prepared analogously to **12a** using methyl (S)-5-(benzyloxy)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate hydrochloride **41** (55 mg, 0.15 mmol) and 2-chloro-6-(trifluoromethyl)benzo[d]oxazole (34 mg, 0.15 mmol) to provide methyl (S)-5-(benzyloxy)-6-methoxy-2-(6-(trifluoromethyl)benzo[d]oxazol-2-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate as crude without purification (80 mg).

MS *m*/*z* (ESI): calcd for $C_{27}H_{24}F_3N_2O_5$ $[M+H]^+$, 513.2; found, 512.8.

Step 2

Prepared analogously to **12** using methyl (S)-5-(benzyloxy)-6-methoxy-2-(6-(trifluoromethyl)benzo[d]oxazol-2-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate **16a** (80 mg, 0.16 mmol) to provide (S)-5-(benzyloxy)-6-methoxy-2-(6-(trifluoromethyl)benzo[d]oxazol-2-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (44 mg, 57% for two steps).

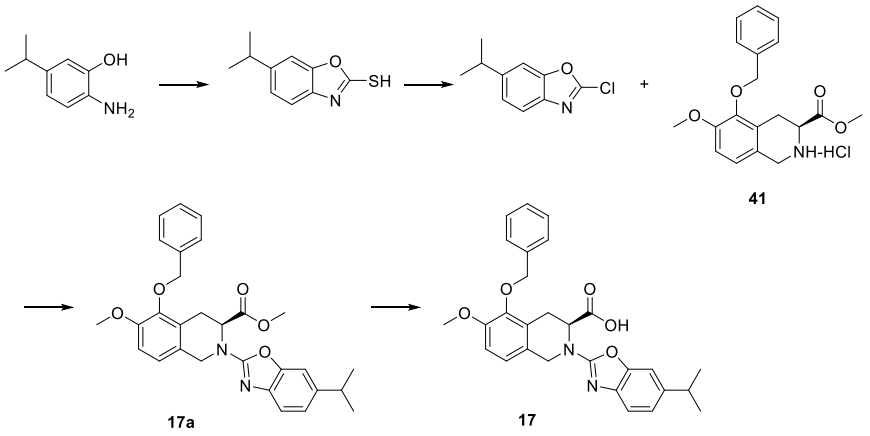
MS *m*/*z* (ESI): calcd for $C_{26}H_{22}F_3N_2O_5$ $[M+H]^+$, 499.2; found, 498.9.

HPLC: Purity > 99%.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.89 (s, 1H), 7.56-7.40 (m, 7H), 7.09 (d, *J* = 8.8 Hz, 1H), 7.02 (d, *J* = 8.4 Hz, 1H), 5.14 (dd, *J* = 6.2, 2.6 Hz, 1H), 4.99 (d, *J* = 10.8 Hz, 1H),

4.88-4.80 (m, 2H), 4.72 (d, *J* = 15.6 Hz, 1H), 3.84 (s, 3H), 3.55 (dd, *J* = 16.2, 2.6 Hz, 1H), 3.02 (dd, *J* = 16.4, 6.4 Hz, 1H).

(S)-5-(Benzyloxy)-2-(6-isopropylbenzo[d]oxazol-2-yl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (17)



Step 1

2-Amino-5-isopropylphenol (220 mg, 1.45 mmol) and potassium ethylxanthate (350 mg, 2.18 mmol) was dissolved in DMF (3 mL). The reaction was heated to 110℃ for 4 hours. The mixture was cooled to room temperature and poured into water (10 mL). 2N HCl was added to adjust pH to about 3. The precipitate was collected and dried to provide 6-isopropylbenzo[d]oxazole-2-thiol as yellow solid (110 mg, 39%).

MS *m*/*z* (ESI): calcd for $C_{10}H_{12}NOS$ $[M+H]^+$, 194.1; found, 193.9.

Step 2

6-Isopropylbenzo[d]oxazole-2-thiol (30 mg, 0.16 mmol) was dissolved in thionyl chloride (3 mL) and heated to reflux for 4 hours. The solution was cooled to room temperature, concentrated to provide 2-chloro-6-isopropylbenzo[d]oxazole as crude without purification (30 mg).

MS *m*/*z* (ESI): calcd for $C_{10}H_{11}ClNO$ $[M+H]^+$, 196.1; found, 195.9.

Step 3

Prepared analogously to **12a** using methyl (S)-5-(benzyloxy)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate hydrochloride **41** (50 mg, 0.14 mmol) and 2-chloro-6-isopropylbenzo[d]oxazole (30 mg) to provide methyl (S)-5-(benzyloxy)-2-(6-isopropylbenzo[d]oxazol-2-yl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (50 mg, 66% for two steps).

MS *m/z* (ESI): calcd for $C_{29}H_{31}N_2O_5$ $[M+H]^+$, 487.2; found, 486.9.

Step 4

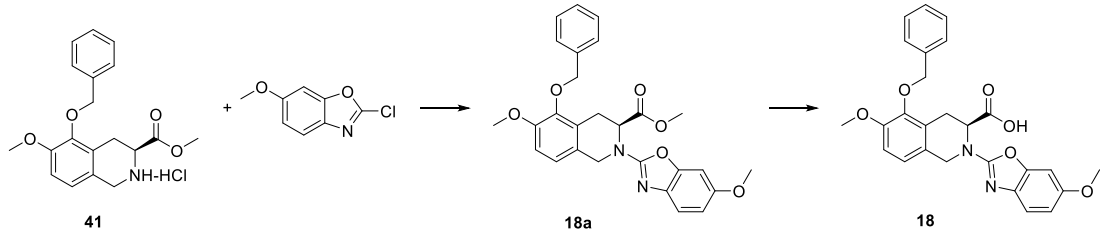
Prepared analogously to **12** using methyl (S)-5-(benzyloxy)-2-(6-isopropylbenzo[d]oxazol-2-yl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate **17a** (50 mg, 0.10 mmol) to provide (S)-5-(benzyloxy)-2-(6-isopropylbenzo[d]oxazol-2-yl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (20 mg, 41%).

MS *m/z* (ESI): calcd for $C_{28}H_{29}N_2O_5$ $[M+H]^+$, 473.2; found, 473.0.

HPLC: Purity > 99%.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.50-7.36 (m, 6H), 7.25 (d, *J* = 8.0 Hz, 1H), 7.09-7.06 (m, 2H), 7.02 (d, *J* = 8.4 Hz, 1H), 5.10 (dd, *J* = 6.4, 2.4 Hz, 1H), 4.99 (d, *J* = 10.8 Hz, 1H), 4.88 (d, *J* = 10.8 Hz, 1H), 4.79 (d, *J* = 16.0 Hz, 1H), 4.66 (d, *J* = 15.6 Hz, 1H), 3.85 (s, 3H), 3.55- 3.54 (m, 1H), 3.03- 2.93 (m, 2H), 1.23 (d, *J* = 6.8 Hz, 6H).

(S)-5-(Benzyloxy)-6-methoxy-2-(6-methoxybenzo[d]oxazol-2-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (18)



41 18a 18

Step 1

Prepared analogously to **12a** using methyl (S)-5-(benzyloxy)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate hydrochloride **41** (200 mg, 0.550 mmol) and 2-chloro-6-methoxybenzo[d]oxazole (121 mg, 0.659 mmol) to provide methyl (S)-5-(benzyloxy)-6-methoxy-2-(6-methoxybenzo[d]oxazol-2-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate as crude without purification (260 mg).

MS *m/z* (ESI): calcd for $C_{27}H_{27}N_2O_6$ $[M+H]^+$, 475.2; found, 474.9.

Step 2

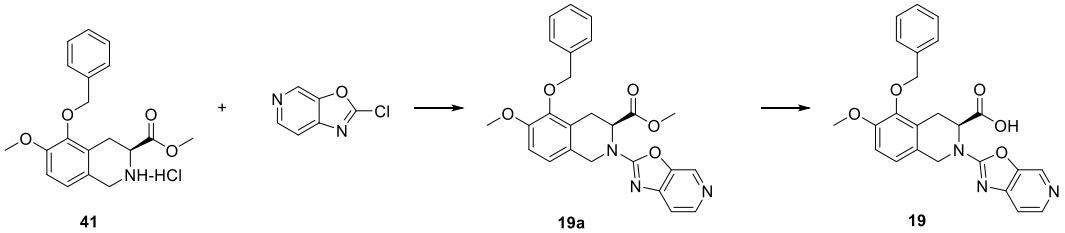
Prepared analogously to **12** using methyl (S)-5-(benzyloxy)-6-methoxy-2-(6-methoxybenzo[d]oxazol-2-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate **18a** (260 mg, 0.548 mmol) to provide (S)-5-(benzyloxy)-6-methoxy-2-(6-methoxybenzo[d]oxazol-2-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (100 mg, 40% for two steps).

MS *m/z* (ESI): calcd for $C_{26}H_{25}N_2O_6$ $[M+H]^+$, 461.2; found, 460.9.

HPLC: Purity > 99%.

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.99 (s, 1H), 7.48-7.36 (m, 5H), 7.24 (d, *J* = 8.4 Hz, 1H), 7.16 (d, *J* = 2.0 Hz, 1H), 7.06 (d, *J* = 8.8 Hz, 1H), 7.01 (d, *J* = 8.4 Hz, 1H), 6.79 (dd, *J* = 8.4, 2.4 Hz, 1H), 5.06 (dd, *J* = 6.2, 2.6 Hz, 1H), 4.98 (d, *J* = 11.2 Hz, 1H), 4.86 (d, *J* = 10.8 Hz, 1H), 4.76 (d, *J* = 16.0 Hz, 1H), 4.64 (d, *J* = 15.6 Hz, 1H), 3.84 (s, 3H), 3.76 (s, 3H), 3.50 (dd, *J* = 15.8, 2.2 Hz, 1H), 2.99 (dd, *J* = 16.6, 5.8 Hz, 1H).

(S)-5-(Benzyloxy)-6-methoxy-2-(oxazolo[5,4-c]pyridin-2-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (19)



41 19a 19

Step 1

Prepared analogously to **12a** using methyl (S)-5-(benzyloxy)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate hydrochloride (50 mg, 0.14 mmol) and 2-chlorooxazolo[5,4-c]pyridine **41** (26 mg, 0.16 mmol) to provide methyl (S)-5-(benzyloxy)-6-methoxy-2-(oxazolo[5,4-c]pyridin-2-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate as crude without purification (60 mg).

MS *m*/*z* (ESI): calcd for $C_{25}H_{24}N_3O_5$ $[M+H]^+$, 446.2; found, 445.9.

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.05 (s, 1H), 8.57 (s, 1H), 7.73 (s, 1H), 7.49-7.35 (m, 5H), 7.12 (d, *J* = 8.8 Hz, 1H), 7.04 (d, *J* = 8.0 Hz, 1H), 5.35 (dd, *J* = 5.8, 3.0 Hz, 1H), 5.02 (d, *J* = 11.2 Hz, 1H), 4.93-4.81 (m, 3H), 3.85 (s, 3H), 3.59 (s, 3H), 3.54 (dd, *J* = 16.4, 2.8 Hz, 1H), 3.08 (dd, *J* = 16.0, 6.0 Hz, 1H)

Step 2

Prepared analogously to **12** using methyl (S)-5-(benzyloxy)-6-methoxy-2-(oxazolo[5,4-c]pyridin-2-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate **19a** (60 mg, 0.14 mmol) to provide (S)-5-(benzyloxy)-6-methoxy-2-(oxazolo[5,4-c]pyridin-2-yl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (7 mg, 12% for two steps).

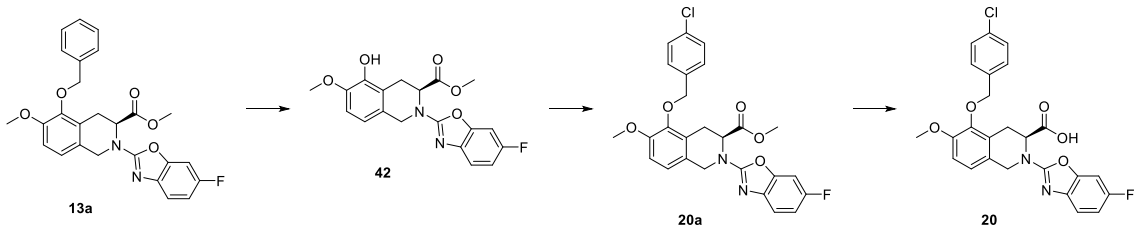
MS *m*/*z* (ESI): calcd for $C_{24}H_{22}N_3O_5$ $[M+H]^+$, 432.2; found, 431.9.

HPLC: Purity 96.8%.

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.05 (s, 1H), 8.55 (d, *J* = 6.4 Hz, 1H), 7.74 (d, *J* = 6.0 Hz, 1H), 7.50-7.36 (m, 5H), 7.13 (d, *J* = 8.0Hz, 1 H), 7.05 (d, *J* = 8.0 Hz, 1H), 5.22 (s,

1H), 5.01 (d, *J* = 11.2 Hz, 1H), 4.92- 4.82 (m, 3H), 3.86 (s, 3H), 3.59 (dd, *J* = 16.2, 2.2 Hz, 1H), 3.05 (dd, *J* = 16.4, 6.0 Hz, 1H).

(S)-5-((4-Chlorobenzyl)oxy)-2-(6-fluorobenzo[d]oxazol-2-yl)-6-methoxy-1,2,3,4-tetra hydroisoquinoline-3-carboxylic acid (20)



Step 1

Methyl (S)-5-(benzyloxy)-2-(6-fluorobenzo[d]oxazol-2-yl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (600 mg, 1.30 mmol) was dissolved in methanol (10 mL). Palladium on charcoal (10%, 300 mg) was added. The reaction was stirred under 1 atm of hydrogen at room temperature overnight. The solution was filtered and the filter cake was washed with EtOAc/methanol (v: v = 1: 1, 100 mL) and CH_2Cl_2 (100 mL). The filtrate was concentrated to provide methyl (S)-2-(6-fluorobenzo[d]oxazol-2-yl)-5-hydroxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate as crude (500 mg).

MS *m*/*z* (ESI): calcd for $C_{19}H_{18}FN_2O_5$ $[M+H]^+$, 373.1; found, 372.9.

Chiral HPLC: retension time, 14.49 min, ee = 99.7% (chromatographic column: ChiralPak IC, 250 × 4.6 mm, 5 μm; T = 25 ℃; λ = 240 nM; mobile phase: Hexane/^{i}PrOH/DEA = 70/30/0.1 (V/V/V); F = 0.8 mL/min; retension time for enantiomers, 13.05 min, 14.49 min).

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.86 (br, 1H), 7.50 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.35 (dd, *J* = 8.6, 5.4 Hz, 1H), 7.10-7.04 (m, 1H), 6.88 (d, *J* = 8.4 Hz, 1H), 6.74 (d, *J* = 8.4 Hz, 1H), 5.25 (dd, *J* = 6.4, 2.4 Hz, 1H), 4.81 (d, *J* = 15.2 Hz, 1H), 4.63 (d, *J* = 15.6 Hz, 1H), 3.79 (s, 3H), 3.59 (s, 3H), 3.46 (dd, *J* = 16.2, 1.8 Hz, 1H), 3.04 (dd, *J* = 16.8, 6.4 Hz, 1H).

Step 2

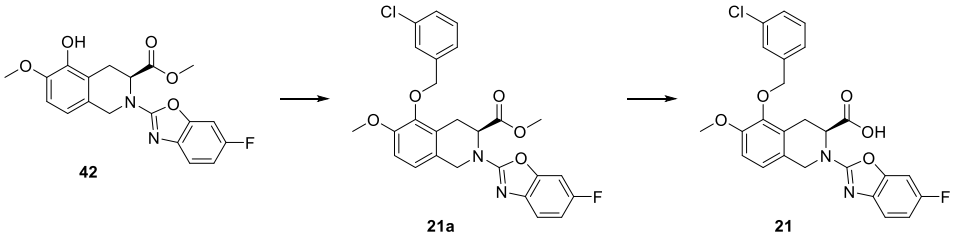
Methyl (S)-2-(6-fluorobenzo[d]oxazol-2-yl)-5-hydroxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (100 mg, 0.269 mmol), 4-chlorobenzyl alcohol (46.2 mg, 0.323 mmol) and triphenylphosphine (106 mg, 0.402 mmol) was dissolved in tetrahydrofuran (5 mL). Diisopropyl azodicarboxylate (92.7 mg, 0.459 mmol) was added. The reaction was stirred at room temperature overnight. The solution was concentrated and purified by silica gel chromatography to provide methyl (S)-5-((4-chlorobenzyl)oxy)-2-(6-fluorobenzo[d]oxazol-2-yl)-6-methoxy-1,2,3,4-tetrahyd

roisoquinoline-3-carboxylate (130 mg, 98%).
MS *m*/*z* (ESI): calcd for $C_{26}H_{23}ClFN_2O_5$ $[M+H]^+$, 497.1; found, 496.9.

Step 3

Methyl (S)-5-((4-chlorobenzyl)oxy)-2-(6-fluorobenzo[d]oxazol-2-yl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (130 mg, 0.254 mmol) and lithium hydroxide monohydrate (10.6 mg, 0.252 mmol) were dissolved in tetrahydrofuran/water (4 mL, volume: 1/1). The reaction was stirred at room temperature overnight. The solution was acidified with 1N HCl and extracted with EtOAc (50 mL×3). The conbined organic phase was washed with saturated aqueous NaCl (50 mL×2), dried over Na_2SO_4, filtered and concentrated. The residue was purified by preparative chromatography to provide (S)-5-((4-chlorobenzyl)oxy)-2-(6-fluorobenzo[d]oxazol-2-yl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (18 mg, 15%).
MS *m*/*z* (ESI): calcd for $C_{25}H_{21}ClFN_2O_5$ $[M+H]^+$, 483.1; found, 482.9.
HPLC: Purity >99%.
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.51-7.45 (m, 5H), 7.32 (dd, *J* = 8.8, 5.2 Hz, 1H), 7.07-6.98 (m, 3H), 5.02 (d, *J* = 4.0 Hz, 1H), 4.96 (d, *J* = 10.8 Hz, 1H), 4.87 (d, *J* = 11.2 Hz, 1H), 4.77 (d, *J* = 15.2 Hz, 1H), 4.67 (d, *J* = 16.0 Hz, 1H), 3.82 (s, 3H), 3.55 (m, 1H), 2.97 (dd, *J* = 16.4, 6.4 Hz, 1H).

(S)-5-((3-Chlorobenzyl)oxy)-2-(6-fluorobenzo[d]oxazol-2-yl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (21)



Step 1

Prepared analogously to **20a** using methyl (S)-2-(6-fluorobenzo[d]oxazol-2-yl)-5-hydroxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate **42** (100 mg, 0.269 mmol) and 3-chlorobenzyl alcohol (46.2 mg, 0.323 mmol) to provide methyl (S)-5-((3-chlorobenzyl)oxy)-2-(6-fluorobenzo[d]oxazol-2-yl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (80 mg, 60%).
MS *m*/*z* (ESI): calcd for $C_{26}H_{23}ClFN_2O_5$ $[M+H]^+$, 497.1; found, 496.8.

Step 2

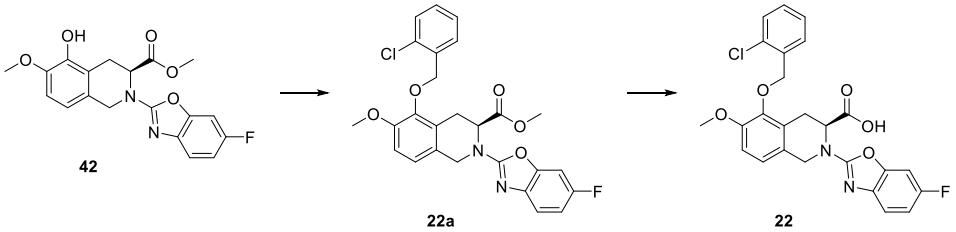
Prepared analogously to **20** using methyl (S)-5-((3-chlorobenzyl)oxy)-2-(6-fluorobenzo[d]oxazol-2-yl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate **21a** (80 mg, 0.16 mmol) to provide (S)-5-((3-chlorobenzyl)oxy)-2-(6-fluorobenzo[d]oxazol-2-yl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (10 mg, 11%).

MS *m*/*z* (ESI): calcd for $C_{25}H_{21}ClFN_2O_5$ $[M+H]^+$, 483.1; found, 482.8.

HPLC: Purity 98.5%.

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.55 (s, 1H), 7.49-7.43 (m, 4H), 7.32 (dd, *J* = 8.4, 4.8 Hz, 1H), 7.07-7.00 (m, 3H), 5.03 (d, *J* = 4.8 Hz, 1H), 4.98 (d, *J* = 11.6 Hz, 1H), 4.88 (d, *J* = 11.2 Hz, 1H), 4.79 (d, *J* = 15.6 Hz, 1H), 4.69 (d, *J* = 15.6 Hz, 1H), 3.83 (s, 3H), 3.56 (d, *J* = 15.6 Hz, 1H), 3.00 (dd, *J* = 15.8, 6.6 Hz, 1H)

(S)-5-((2-Chlorobenzyl)oxy)-2-(6-fluorobenzo[d]oxazol-2-yl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (22)



Step 1

Methyl (S)-2-(6-fluorobenzo[d]oxazol-2-yl)-5-hydroxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (60 mg, 0.16 mmol) was dissolved in DMF (5 mL). 2-Chlorobenzyl chloride (34 mg, 0.21 mmol), Potassium carbonate (33 mg, 0.24 mmol) and sodium iodide (36 mg, 0.24 mmol) were added. The reaction was stirred at room temperature overnight. EtOAc (100 mL) and water (80 mL) were added and separated. The aqueous phase was extracted by EtOAc (100 mL×2). The combined organic phase washed with saturated aqueous NaCl (50 mL×2), dried over Na_2SO_4, filtered and concentrated to provide methyl (S)-5-((2-chlorobenzyl)oxy)-2-(6-fluorobenzo[d]oxazol-2-yl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate as crude (70 mg, 80%).

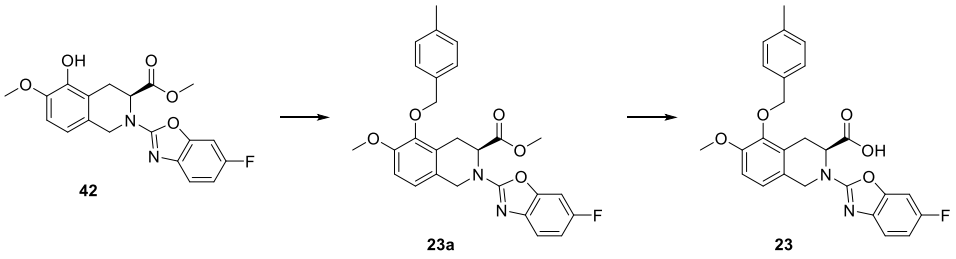
MS *m*/*z* (ESI): calcd for $C_{26}H_{23}ClFN_2O_5$ $[M+H]^+$, 497.1; found, 496.9.

Step 2

Prepared analogously to **20** using methyl (S)-5-((2-chlorobenzyl)oxy)-2-(6-fluorobenzo[d]oxazol-2-yl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate **22a** (70 mg, 0.14 mmol) to provide (S)-5-((2-chlorobenzyl)oxy)-2-(6-fluorobenzo[d]oxazol-2-yl)-6-methoxy-1,2,3,4-tetrahyd

roisoquinoline-3-carboxylic acid (10 mg, 15%).
MS *m*/*z* (ESI): calcd for $C_{25}H_{21}ClFN_2O_5$ $[M+H]^+$, 483.1; found, 482.9.
HPLC: Purity 95.8%.
^{1}H NMR (400 MHz, DMSO-d_6) δ 13.03 (br, 1H), 7.66-7.64 (m, 1H), 7.53-7.48 (m, 2H), 7.45-7.41 (m, 2H), 7.34 (dd, *J* = 8.8, 4.8 Hz, 1H), 7.10-7.02 (m, 3H), 5.09-5.05 (m, 2H), 5.01 (d, *J* = 11.6 Hz, 1H), 4.79 (d, *J* = 15.6 Hz, 1H), 4.67 (d, *J* = 15.6 Hz, 1H), 3.84 (s, 3H), 3.51 (dd, *J* = 16.4, 2.8 Hz, 1H), 2.99 (dd, *J* = 16.2, 6.6 Hz, 1H).

(S)-2-(6-Fluorobenzo[d]oxazol-2-yl)-6-methoxy-5-((4-methylbenzyl)oxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (23)



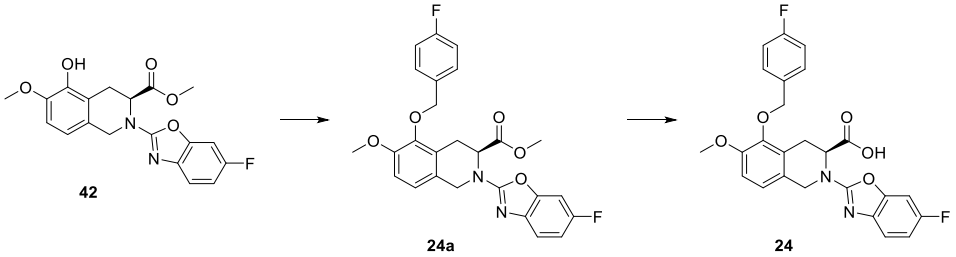
Step 1
Prepared analogously to **20a** using methyl (S)-2-(6-fluorobenzo[d]oxazol-2-yl)-5-hydroxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate **42** (100 mg, 0.269 mmol) and 4-Methylbenzyl alcohol (36.1 mg, 0.295 mmol) to provide methyl (S)-2-(6-fluorobenzo[d]oxazol-2-yl)-6-methoxy-5-((4-methylbenzyl)oxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (120 mg, 94%).
MS *m*/*z* (ESI): calcd for $C_{27}H_{26}FN_2O_5$ $[M+H]^+$, 477.2; found, 476.9.

Step 2
Prepared analogously to **20** using methyl (S)-2-(6-fluorobenzo[d]oxazol-2-yl)-6-methoxy-5-((4-methylbenzyl)oxy)-1,2,3,4- tetrahydroisoquinoline-3-carboxylate **23a** (120 mg, 0.252 mmol) to (S)-2-(6-fluorobenzo[d]oxazol-2-yl)-6-methoxy-5-((4-methylbenzyl)oxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (20 mg, 17%).
MS *m*/*z* (ESI): calcd for $C_{26}H_{24}FN_2O_5$ $[M+H]^+$, 463.2; found, 462.9.
HRMS *m*/*z* (ESI): calcd for $C_{26}H_{24}FN_2O_5$ $[M+H]^+$, 463.1669; found, 463.1670.
HPLC: Purity 97.8%.
$[\alpha]_D^{20}$ + 36.2 (*c* 1.00, MeOH).
^{1}H NMR (400 MHz, DMSO-d_6) δ 13.05 (br, 1H), 7.49 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.36-7.31 (m, 3H), 7.21 (d, *J* = 8.0 Hz, 2H), 7.08-6.99 (m, 3H), 5.06 (dd, *J* = 6.0, 2.8 Hz, 1H), 4.93 (d, *J* = 10.4 Hz, 1H), 4.81 (d, *J* = 10.8 Hz, 1H), 4.77 (d, *J* = 15.6 Hz, 1H), 4.65

(d, *J* = 15.2 Hz, 1H), 3.83 (s, 3H), 3.50 (dd, *J* = 16.2, 2.2 Hz, 1H), 2.97 (dd, *J* = 16.2, 6.2 Hz, 1H), 2.32 (s, 3H).

^{13}C NMR (100 MHz, DMSO-d_6) δ 172.45, 162.70, 157.63 (d, *J* = 234.7 Hz), 151.45, 148.57 (d, *J* = 15.0 Hz), 145.00, 139.61, 137.71, 134.98, 129.37, 128.80, 126.37, 125.04, 122.38, 116.40 (d, *J* = 9.6 Hz), 112.11, 111.32 (d, *J* = 23.5 Hz), 98.55 (d, *J* = 28.8 Hz), 74.42, 56.34, 54.41, 45.18, 25.39, 21.29.

(S)-2-(6-Fluorobenzo[d]oxazol-2-yl)-5-((4-fluorobenzyl)oxy)-6-methoxy-1,2,3,4-tetra hydroisoquinoline-3-carboxylic acid (24)



Step 1

Prepared analogously to **20a** using methyl (S)-2-(6-fluorobenzo[d]oxazol-2-yl)-5-hydroxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate **42** (100 mg, 0.269 mmol) and 4-fluorobenzyl alcohol (40.7 mg, 0.322 mmol) to provide methyl (S)-2-(6-fluorobenzo[d]oxazol-2-yl)-5-((4-fluorobenzyl)oxy)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (100 mg, 77%).

MS *m*/*z* (ESI): calcd for $C_{26}H_{23}F_2N_2O_5$ $[M+H]^+$, 481.2; found, 480.9.

Step 2

Prepared analogously to **20** using methyl (S)-2-(6-fluorobenzo[d]oxazol-2-yl)-5-((4-fluorobenzyl)oxy)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate **24a** (100 mg, 0.21 mmol) to provide (S)-2-(6-fluorobenzo[d]oxazol-2-yl)-5-((4-fluorobenzyl)oxy)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (20 mg, 21%).

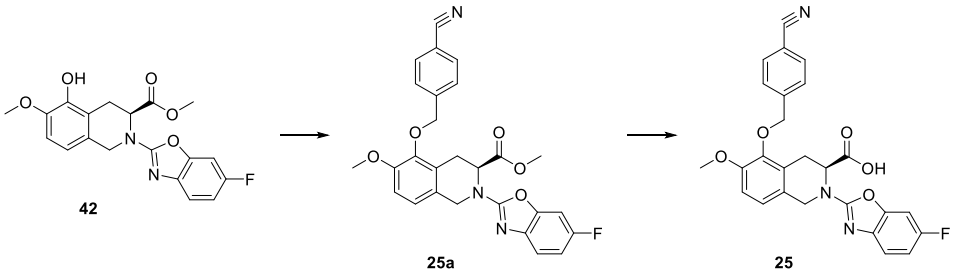
MS *m*/*z* (ESI): calcd for $C_{25}H_{21}F_2N_2O$ $[M+H]^+$, 467.1; found, 466.9.

HPLC: Purity 96.3%.

^{1}H NMR (400 MHz, DMSO-d_6) δ 13.10 (s, 1H), 7.52-7.47 (m, 3H), 7.33 (dd, *J* = 8.4, 5.2 Hz, 1H), 7.23 (t, *J* = 8.8 Hz, 2H), 7.08-6.99(m, 3H), 5.06 (d, *J* = 4.0 Hz, 1H), 4.95 (d, *J* = 10.8 Hz, 1H), 4.85 (d, *J* = 10.8 Hz, 1H), 4.77 (d, *J* = 16.0 Hz, 1H), 4.66 (d, *J* = 16.0 Hz, 1H), 3.83 (s, 3H), 3.50 (dd, *J* = 16.0, 2.4 Hz, 1H), 2.97 (dd, *J* = 15.8, 6.6 Hz, 1H).

(S)-5-((4-Cyanobenzyl)oxy)-2-(6-fluorobenzo[d]oxazol-2-yl)-6-methoxy-1,2,3,4-tetra

hydroisoquinoline-3-carboxylic acid (25)



Step 1

Methyl (S)-2-(6-fluorobenzo[d]oxazol-2-yl)-5-hydroxy-6-methoxy-1,2,3,4-tetrahydro-isoquinoline-3-carboxylate (100 mg, 0.269 mmol) was dissolved in DMF (5 mL). *p*-Cyanobenzyl chloride (49 mg, 0.32 mmol) and potassium carbonate (193 mg, 1.40 mmol) were added. The reaction was heated to 75℃ for 4 hours. EtOAc (100 mL) and water (100 mL) were added and separated. The aqueous phase was extracted by EtOAc (50 mL×2). The combined organic phase washed with saturated aqueous NaCl (20 mL×2), dried over Na_2SO_4, filtered and concentrated to provide methyl (S)-5-((4-cyanobenzyl)oxy)-2-(6-fluorobenzo[d]oxazol-2-yl)-6-methoxy-1,2,3,4-tetrahyd roisoquinoline-3-carboxylate as crude (130 mg, 99%).

MS *m/z* (ESI): calcd for $C_{27}H_{23}FN_3O_5$ $[M+H]^+$, 488.2; found, 487.9.

Step 2

Methyl (S)-5-((4-cyanobenzyl)oxy)-2-(6-fluorobenzo[d]oxazol-2-yl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (130 mg, 0.267 mmol) was dissolved in tetrahydrofuran (4 mL). The solution of calcium chloride (482 mg, 4.34 mmol) in isopropanol/water (3 mL, volume: 2/1) was added. The solution of sodium hydroxide (56 mg, 1.4 mmol) in water (3 mL) was added dropwise. The reaction was stirred at room temperature overnight. EtOAc (80 mL) and water (150 mL) were added. The solution was acidified with 1N HCl to adjust pH to about 5. The organic phase was separated. The aqueous phase was washed with EtOAc (50 mL×2). The combined organic phase was washed with saturated aqueous NaCl (50 mL×2), dried over Na_2SO_4, filtered and concentrated. The residue was purified by preparative chromatography to provide (S)-5-((4-cyanobenzyl)oxy)-2-(6-fluorobenzo[d]oxazol-2-yl)-6-methoxy-1,2,3,4-tetrahydroiso-quinoline-3-carboxylic acid (20 mg, 16 %).

MS *m/z* (ESI): calcd for $C_{26}H_{21}FN_3O_5$ $[M+H]^+$, 474.2; found, 473.9.

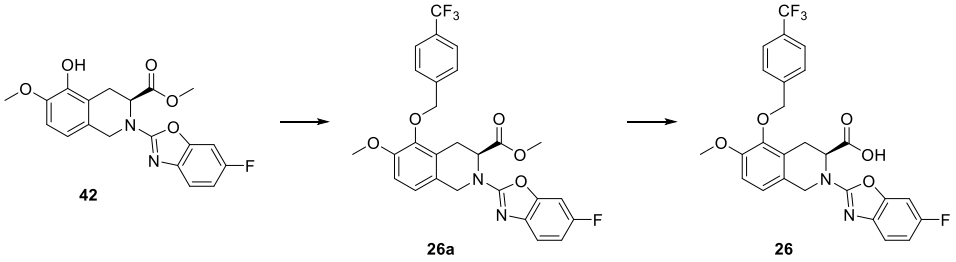
HRMS *m/z* (ESI): calcd for $C_{26}H_{21}FN_3O_5$ $[M+H]^+$, 474.1465; found, 474.1460.

HPLC: Purity > 99%.

$[\alpha]_D^{20}$ + 41.7 (*c* 1.00, MeOH).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.89 (d, J = 8.0 Hz, 2H), 7.68 (d, J = 8.0 Hz, 2H), 7.49 (dd, J = 8.4, 2.8 Hz, 1H), 7.34 (dd, J = 8.6, 5.0 Hz, 1H), 7.09-7.01 (m, 3H), 5.11-5.07 (m, 2H), 4.98 (d, J = 12.4 Hz, 1H), 4.79 (d, J = 16.0 Hz, 1H), 4.67 (d, J = 15.6 Hz, 1H), 3.82 (s, 3H), 3.51 (dd, J = 16.6, 2.6 Hz, 1H), 3.04 (dd, J = 16.4, 6.4 Hz, 1H).
^{13}C NMR (100 MHz, DMSO-d_6) δ 172.34, 162.69, 162.66, 157.65 (d, J = 235.0 Hz), 151.25, 148.58 (d, J = 14.9 Hz), 143.65, 139.58, 132.84, 128.92, 126.24, 125.05, 122.74, 119.27, 116.43 (d, J = 9.6 Hz), 112.11, 111.34 (d, J = 23.6 Hz), 111.08, 98.56 (d, J = 28.8 Hz), 73.45, 56.33, 54.33, 45.14, 25.33.

(S)-2-(6-Fluorobenzo[d]oxazol-2-yl)-6-methoxy-5-((4-(trifluoromethyl)benzyl)oxy)-1, 2,3,4-tetrahydroisoquinoline-3-carboxylic acid (26)



Step 1

Prepared analogously to **25a** using methyl (S)-2-(6-fluorobenzo[d]oxazol-2-yl)-5-hydroxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate **42** (100 mg, 0.269 mmol) and 4-(trifluoromethyl)benzyl chloride (58 mg, 0.30 mmol) to provide methyl (S)-2-(6-fluorobenzo[d]oxazol-2-yl)-6-methoxy-5-((4-(trifluoromethyl)benzyl)oxy)-1,2,3 ,4-tetrahydroisoquinoline-3-carboxylate as crude (143 mg, 100%).
MS m/z (ESI): calcd for $C_{27}H_{23}F_4N_2O$ $[M+H]^+$, 531.2; found, 530.9.

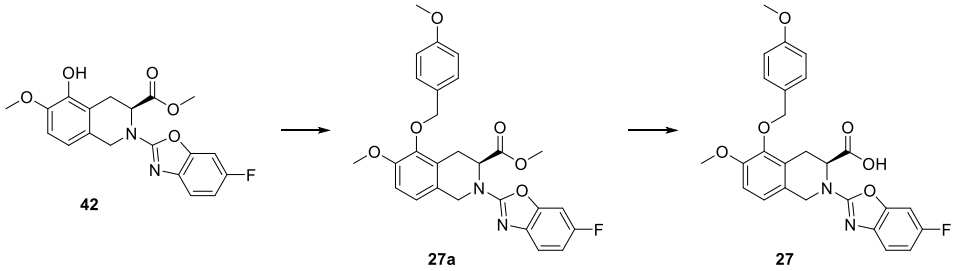
Step 1

Prepared analogously to **25** using methyl (S)-2-(6-fluorobenzo[d]oxazol-2-yl)-6-methoxy-5-((4-(trifluoromethyl)benzyl)oxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate **26a** (143 mg, 0.270 mmol) to provide (S)-2-(6-fluorobenzo[d]oxazol-2-yl)-6-methoxy-5-((4-(trifluoromethyl)benzyl)oxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (60 mg, 43%).
MS m/z (ESI): calcd for $C_{26}H_{21}F_4N_2O_5$ $[M+H]^+$, 517.1; found, 516.8.
HRMS m/z (ESI): calcd for $C_{26}H_{21}F_4N_2O_5$ $[M+H]^+$, 517.1387; found, 517.1384.
HPLC: Purity 98.8%.
$[\alpha]_D^{20}$ + 48.3 (c 1.00, MeOH).
^{1}H NMR (400 MHz, DMSO-d_6) δ 13.06 (br, 1H), 7.79 (d, J = 8.4 Hz, 2H), 7.71 (d, J =

8.0 Hz, 2H), 7.49 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.33 (dd, *J* = 8.4, 5.2 Hz, 1H), 7.09-7.01 (m, 3H), 5.10-5.07 (m, 2H), 4.97 (d, *J* = 11.6 Hz, 1H), 4.79 (d, *J* = 15.2 Hz, 1H), 4.67 (d, *J* = 15.6 Hz, 1H), 3.82 (s, 3H), 3.52 (dd, *J* = 16.2, 2.2 Hz, 1H), 3.05 (dd, *J* = 16.2, 6.2 Hz, 1H).

^{13}C NMR (100 MHz, DMSO-d_6) δ 172.35, 162.68 (d, *J* = 2.0 Hz), 157.65 (d, *J* = 234.9 Hz), 151.28, 148.58 (d, *J* = 14.8 Hz), 144.77, 142.78, 139.59, 128.91 (q, *J* = 31.5 Hz), 128.84, 126.24, 125.73 (q, *J* = 3.8 Hz), 125.05, 124.74 (q, *J* = 270.5 Hz), 122.69, 116.42 (d, *J* = 9.6 Hz), 112.10, 111.32 (d, *J* = 28.8 Hz), 98.54 (d, *J* = 28.8 Hz), 73.54, 56.31, 54.34, 45.15, 25.34.

(S)-2-(6-fluorobenzo[d]oxazol-2-yl)-6-methoxy-5-((4-methoxybenzyl)oxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (27)



Step 1

Prepared analogously to **20a** using methyl (S)-2-(6-fluorobenzo[d]oxazol-2-yl)-5-hydroxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate **42** (1.0 g, 2.7 mmol) and 4-methoxybenzyl alcohol (0.48 g, 3.4 mmol) to provide methyl (S)-2-(6-fluorobenzo[d]oxazol-2-yl)-6-methoxy-5-((4-methoxybenzyl)oxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (1.2 g, 91%).

MS *m*/*z* (ESI): calcd for $C_{27}H_{26}FN_2O_6$ $[M+H]^+$, 493.2; found, 492.9.

Chiral HPLC: retension time, 21.32 min, ee = 99.7% (chromatographic column: Chiralcel OD-RH, 150 × 4.6 mm, 5 μm; T = 25 ℃; λ = 234 nM; mobile phase: Acetonitril/50 mM KPF_6 (adjust pH to 2.0 with H_3PO_4) = 60/40 (V/V); F = 0.8 mL/min; retension time for enantiomers, 21.32 min, 24.15 min)

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.50 (dd, *J* = 8.4, 2.8 Hz, 1H), 7.41-7.34 (m, 3H), 7.10-6.95 (m, 5H), 5.19 (dd, *J* = 6.4, 2.8 Hz, 1H), 4.94 (d, *J* = 10.8 Hz, 1H), 4.82-4.77 (m, 2H), 4.66 (d, *J* = 15.6 Hz, 1H), 3.85 (s, 3H), 3.79-3.76 (m, 4H), 3.57 (s, 3H), 3.01 (dd, *J* = 16.4, 6.4 Hz, 1H).

Step 2

Prepared analogously to **25** using methyl (S)-2-(6-fluorobenzo[d]oxazol-2-yl)-6-

methoxy-5-((4-methoxybenzyl)oxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate **27a** (1.2 g, 2.4 mmol) to provide (S)-2-(6-fluorobenzo[d]oxazol-2-yl)-6-methoxy-5-((4-methoxybenzyl)oxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (0.41 g, 35%).

MS *m*/*z* (ESI): calcd for $C_{26}H_{24}FN_2O_6$ $[M+H]^+$, 479.2; found, 478.9.

HRMS *m*/*z* (ESI): calcd for $C_{26}H_{24}FN_2O_6$ $[M+H]^+$, 479.1618; found, 479.1615.

HPLC: Purity 97.6%.

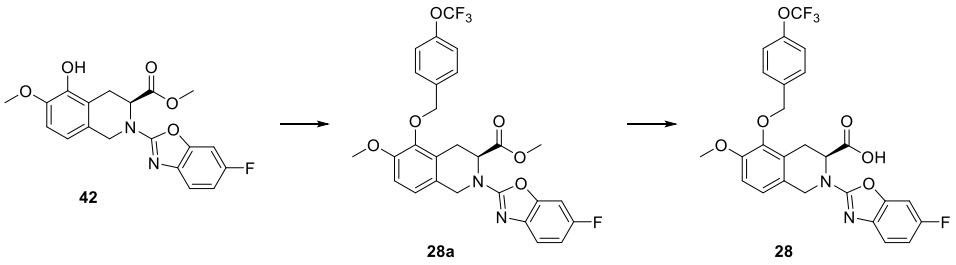
Chiral HPLC: retension time, 20.69 min, ee = 98.2% (chromatographic column: ChiralPak AS-H, 250 × 4.6 mm, 5 μm; T = 25 ℃; λ = 240 nM; mobile phase: Hexane/^{i}PrOH/DEA = 70/30/0.1 (V/V/V); F = 0.8 mL/min; retension time for enantiomers, 11.57 min, 20.69 min).

$[\alpha]_D^{20}$ + 26.4 (*c* 1.00, MeOH).

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.48 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.40-7.32 (m, 3H), 7.08-6.95 (m, 5H), 5.07 (d, *J* = 3.6 Hz, 1H), 4.92 (d, *J* = 10.8 Hz, 1H), 4.82-4.75 (m, 2H), 4.67 (d, *J* = 16.0 Hz, 1H), 3.84 (s, 3H), 3.77 (s, 3H), 3.52 (d, *J* = 14.4, 1H). 2.97 (dd, *J* = 16.6, 6.2 Hz, 1H).

^{13}C NMR (100 MHz, DMSO) δ 172.33, 162.47(d, *J* = 1.91 Hz), 159.73, 157.76(d, *J* = 235.37 Hz), 148.32(d, *J* = 14.75 Hz), 146.34, 143.79, 138.59, 130.79, 124.65, 119.37, 116.90, 116.15(d, *J* = 9.64 Hz), 114.46, 111.48(d, J = 23.70 Hz), 110.98, 98.66(d, *J* = 28.94 Hz), 91.62, 59.69, 56.39, 55.58, 54.43, 45.30, 24.83.

(S)-2-(6-Fluorobenzo[d]oxazol-2-yl)-6-methoxy-5-((4-(trifluoromethoxy)benzyl)oxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (28)



Step 1

Prepared analogously to **25a** using methyl (S)-2-(6-fluorobenzo[d]oxazol-2-yl)-5-hydroxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate **42** (100 mg, 0.269 mmol) and 4-(Trifluoromethoxy)benzyl chloride (63.2 mg, 0.300 mmol) to heat at 70℃ for 4 hours to provide methyl (S)-2-(6-fluorobenzo[d]oxazol-2-yl)-6-methoxy-5-((4-(trifluoromethoxy)benzyl)oxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate as crude (147 mg, 100%).

MS *m*/*z* (ESI): calcd for $C_{27}H_{23}F_4N_2O_6$ $[M+H]^+$, 547.2; found, 546.9.

Step 2

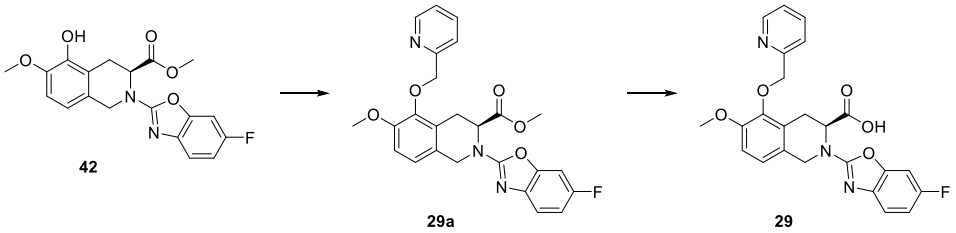
Prepared analogously to **25** using methyl (S)-2-(6-fluorobenzo[d]oxazol-2-yl)-6-methoxy-5-((4-(trifluoromethoxy)benzyl)oxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate **28a** (147 mg, 0.269 mmol) to provide (S)-2-(6-fluorobenzo[d]oxazol-2-yl)-6-methoxy-5-((4-(trifluoromethoxy)benzyl)oxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (60 mg, 42%).

MS *m*/*z* (ESI): calcd for $C_{26}H_{21}F_4N_2O_6$ $[M+H]^+$, 533.1; found, 532.8.

HPLC: Purity 98.9%.

^{1}H NMR (400 MHz, DMSO-d_6) δ 13.06 (br, 1H), 7.61 (d, *J* = 8.4 Hz, 2H), 7.48 (dd, *J* = 8.2, 2.2 Hz, 1H), 7.41 (d, *J* = 8.0 Hz, 2H), 7.33 (dd, *J* = 8.4, 4.8 Hz, 1H), 7.08-7.00 (m, 3H), 5.09 (dd, *J* = 6.4, 2.8 Hz, 1H), 5.01 (d, *J* = 11.2 Hz, 1H), 4.89 (d, *J* = 11.6 Hz, 1H), 4.78 (d, *J* = 16.0 Hz, 1H), 4.66 (d, *J* = 15.6 Hz, 1H), 3.82 (s, 3H), 3.51 (dd, *J* = 16.6, 2.2 Hz, 1H), 3.02 (dd, *J* = 16.0, 6.4 Hz, 1H).

(S)-2-(6-Fluorobenzo[d]oxazol-2-yl)-6-methoxy-5-(pyridin-2-ylmethoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (29)



Step 1

Prepared analogously to **22a** using methyl (S)-2-(6-fluorobenzo[d]oxazol-2-yl)-5-hydroxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate **42** (80 mg, 0.22 mmol) and 2-chloromethylpyridine hydrochloride (280 mg, 1.7 mmol) to provide methyl (S)-2-(6-fluorobenzo[d]oxazol-2-yl)-6-methoxy-5-(pyridin-2-ylmethoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate as crude (50 mg, 50%).

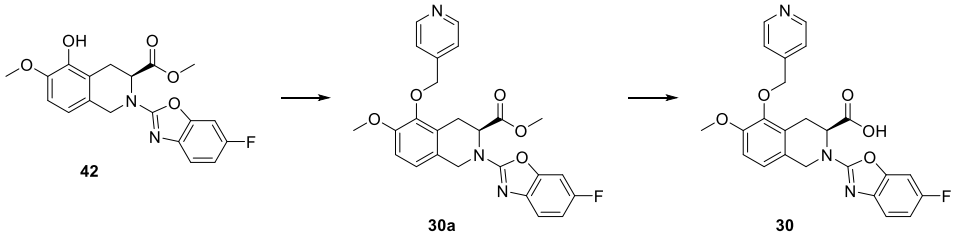
MS *m*/*z* (ESI): calcd for $C_{25}H_{23}FN_3O_5$ $[M+H]^+$, 464.2; found, 463.9.

Step 2

Prepared analogously to **20** using methyl (S)-2-(6-fluorobenzo[d]oxazol-2-yl)-6-methoxy-5-(pyridin-2-ylmethoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate **29a** (50 mg, 0.11 mmol) to provide (S)-2-(6-fluorobenzo[d]oxazol-2-yl)-6-methoxy-5-(pyridin-2-ylmethoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (9 mg, 18%).

MS m/z (ESI): calcd for $C_{24}H_{21}FN_3O_5$ $[M+H]^+$, 450.2; found, 449.9.
HPLC: Purity 98.7%.

(S)-2-(6-Fluorobenzo[d]oxazol-2-yl)-6-methoxy-5-(pyridin-4-ylmethoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (30)



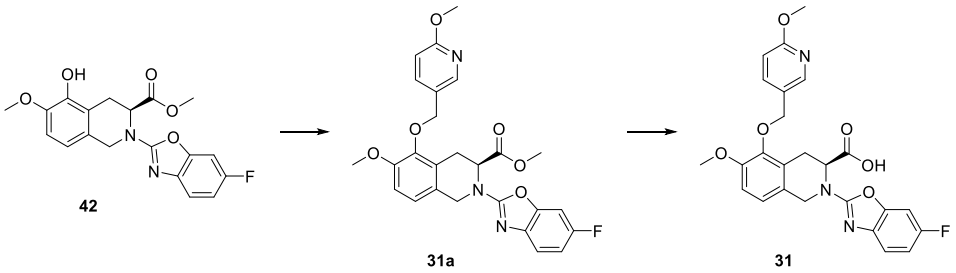
Step 1

Prepared analogously to **25a** using methyl (S)-2-(6-fluorobenzo[d]oxazol-2-yl)-5-hydroxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate **42** (100 mg, 0.269 mmol) and 4-Chloromethylpyridine hydrochloride (128 mg, 0.780 mmol) to provide methyl (S)-2-(6-fluorobenzo[d]oxazol-2-yl)-6-methoxy-5-(pyridin-4-ylmethoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate as crude (140 mg, 100%).
MS *m*/*z* (ESI): calcd for $C_{25}H_{23}FN_3O_5$ $[M+H]^+$, 464.2; found, 463.9.

Step 2

Prepared analogously to **25** using methyl (S)-2-(6-fluorobenzo[d]oxazol-2-yl)-6-methoxy-5-(pyridin-4-ylmethoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate **30a** (125 mg, 0.270 mmol) to provide (S)-2-(6-fluorobenzo[d]oxazol-2-yl)-6-methoxy-5-(pyridin-4-ylmethoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (20 mg, 17 %).
MS *m*/*z* (ESI): calcd for $C_{24}H_{21}FN_3O_5$ $[M+H]^+$, 450.2; found, 450.0.
HRMS *m*/*z* (ESI): calcd for $C_{24}H_{21}FN_3O_5$ $[M+H]^+$, 450.1465; found, 450.1465.
HPLC: Purity 98.8%.
$[\alpha]_D^{20}$ + 30.1 (*c* 1.00, MeOH).
1H NMR (400 MHz, DMSO-d_6) δ 8.78 (br, 2H), 7.80 (br, 2H), 7.49 (dd, *J* = 8.4, 2.6 Hz, 1H), 7.34 (dd, *J* = 8.6, 4.9 Hz, 1H), 7.15 – 6.99 (m, 3H), 5.24 – 5.02 (m, 3H), 4.81 (d, *J* = 15.8 Hz, 1H),4.68 (d, *J* = 15.8 Hz, 1H), 3.81 (s, 3H), 3.53 (dd, *J* = 16.4, 2.7 Hz, 1H), 3.10 (dd, *J* = 16.3, 6.4 Hz, 1H).
^{13}C NMR (100 MHz, DMSO-d_6) δ 172.28, 162.67 (d, *J* = 2.1 Hz), 157.66 (d, *J* = 234.9 Hz), 151.05, 148.57 (d, *J* = 14.88 Hz), 145.69, 144.51, 139.55, 126.14, 125.08, 123.82, 123.01, 116.45 (d, *J* = 9.48 Hz), 112.14, 111.36(d, *J* = 23.59 Hz), 98.57 (d, *J* = 28.71 Hz), 72.32, 56.32, 54.28, 45.10, 25.29.

(S)-2-(6-Fluorobenzo[d]oxazol-2-yl)-6-methoxy-5-((6-methoxypyridin-3-yl)methoxy) -1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (31)



Step 1

Prepared analogously to **25a** using methyl (S)-2-(6-fluorobenzo[d]oxazol-2-yl)-5-hydroxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate **42** (350 mg, 0.940 mmol) and 5-(Chloromethyl)-2-methoxypyridine (500 mg, 3.16 mmol) to provide methyl (S)-2-(6-fluorobenzo[d]oxazol-2-yl)-6-methoxy-5-((6-methoxypyridin-3-yl)methoxy)-1,2 ,3,4-tetrahydroisoquinoline-3-carboxylate as crude(450 mg, 97%).

MS *m*/*z* (ESI): calcd for $C_{26}H_{25}FN_3O_6$ $[M+H]^+$, 494.2; found, 493.9.

Step 2

Prepared analogously to **25** using methyl (S)-2-(6-fluorobenzo[d]oxazol-2-yl)-6-methoxy-5-((6-methoxypyridin-3-yl)methoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxyl ate **31a** (450 mg, 0.91 mmol) to provide (S)-2-(6-fluorobenzo[d]oxazol-2-yl)-6-methoxy-5-((6-methoxypyridin-3-yl)methoxy)-1,2 ,3,4-tetrahydroisoquinoline-3-carboxylic acid (210 mg, 48%).

MS *m*/*z* (ESI): calcd for $C_{25}H_{23}FN_3O_6$ $[M+H]^+$, 480.2; found, 480.2.

HRMS *m*/*z* (ESI): calcd for $C_{25}H_{23}FN_3O_6$ $[M+H]^+$, 480.1571; found, 480.1573.

HPLC: Purity >99%.

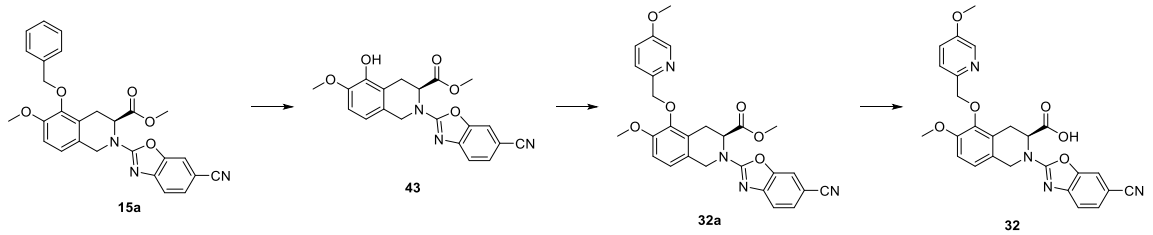
Chiral HPLC: retension time, 53.60 min, ee = 96.1% (chromatographic column: ChiralPak OD-RH, 150 × 4.6 mm, 5 μm; T = 25 ℃; λ = 240 nM; mobile phase: Acetonitril/50 mM KPF_6 (adjust pH to 2.0 with H_3PO_4) = 35/65 (V/V); F = 0.5 mL/min; retension time for enantiomers, 53.60 min, 56.93 min).

$[\alpha]_D^{20}$ + 23.5 (*c* 1.00, MeOH).

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.24 (s, 1H), 7.93 (d, *J* = 8.8 Hz, 1H), 7.30 (dd, *J* = 8.8, 4.4 Hz, 1H), 7.07 (dd, *J* = 8.0, 2.4 Hz, 1H), 6.95- 6.83 (m, 4H), 5.16- 5.14 (m, 1H), 5.04 (d, *J* = 11.2 Hz, 1H), 4.94 (d, *J* = 11.6 Hz, 1H), 4.86 (d, *J* = 15.2 Hz, 1H), 4.80 (d, *J* = 15.2 Hz, 1H), 4.02 (s, 3H), 3.87 (s, 3H), 3.60 (d, *J* = 16.4 Hz, 1H), 2.94 (dd, *J* = 16.6, 2.8 Hz, 1H).

^{13}C NMR (100 MHz, DMSO-d_6) δ 170.40, 161.65, 160.62, 156.10 (d, J = 235.41 Hz), 149.70, 146.64 (d, J = 14.76 Hz), 143.93, 142.96, 140.26, 136.86, 125.35, 124.59, 123.16, 120.91, 114.51 (d, J = 9.48 Hz), 110.41, 109.87 (d, J = 23.67 Hz), 109.38, 97.06 (d, J = 28.87 Hz), 69.76, 54.66, 53.06, 52.86, 43.59, 23.71.

(S)-2-(6-Cyanobenzo[d]oxazol-2-yl)-6-methoxy-5-((5-methoxypyridin-2-yl)methoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (32)



Step 1

Methyl (S)-5-(benzyloxy)-2-(6-cyanobenzo[d]oxazol-2-yl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (1.9 g, 4.1 mmol) was dissolved in tetrahydrofuran (20 mL). Palladium on charcoal (10%, 190 mg) was added. The reaction was stirred under 1 atm of hydrogen at room temperature overnight. The solution was filtered and the filtrate was concentrated to provide methyl (S)-2-(6-cyanobenzo[d]oxazol-2-yl)-5-hydroxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (1.5 g, 98%). The NMR sample was purified by silica gel chromatography.

MS m/z (ESI): calcd for $C_{20}H_{18}N_3O_5$ $[M+H]^+$, 380.1; found, 380.1.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, J = 0.8 Hz, 1H), 7.51 (dd, J = 8.4, 1.2 Hz, 1H), 7.41 (d, J = 8.0 Hz, 1H), 6.80 (d, J = 8.4 Hz, 1H), 6.72 (d, J = 8.4 Hz, 1H), 5.88 (s, 1H), 5.32 (d, J = 4.4 Hz, 1H), 4.97 (d, J = 15.6 Hz, 1H), 4.81 (d, J = 15.6 Hz, 1H), 3.88 (s, 3H), 3.67- 3.63 (m, 4H), 3.13 (dd, J = 16.6, 6.6 Hz, 1H).

Step 2

Methyl (S)-2-(6-cyanobenzo[d]oxazol-2-yl)-5-hydroxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (100 mg, 0.264 mmol) was dissolved in DMF (6 mL). 2-(Chloromethyl)-5-methoxypyridine hydrochloride (122 mg, 0.629 mmol) and potassium carbonate (300 mg, 2.1 mmol) were added. The reaction was heated to 70℃ for 6 hours. EtOAc (30 mL) and water (20 mL) were added and separated. The aqueous phase was extracted by EtOAc (10 mL×2). The combined organic phase washed with saturated aqueous NaCl (15 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by preparative chromatography to provide methyl (S)-2-(6-

cyanobenzo[d]oxazol-2-yl)-6-methoxy-5-((5-methoxypyridin-2-yl)methoxy)-1,2,3,4-tetra hydroisoquinoline-3-carboxylate (100 mg, 76%).

MS *m*/*z* (ESI): calcd for $C_{27}H_{25}N_4O_6$ $[M+H]^+$, 501.2; found, 500.9.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, *J* = 2.4 Hz, 1H), 7.57-7.55 (m, 2H), 7.51 (d, *J* = 8.4 Hz, 1H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.29-7.28 (m, 1H), 6.96 (d, *J* = 8.8 Hz, 1H), 6.88 (d, *J* = 8.8 Hz, 1H), 5.23 (br, 1H), 5.11 (d, *J* = 12.0 Hz, 1H), 5.03 (d, *J* = 11.6 Hz, 1H), 4.94 (d, *J* = 15.6 Hz, 1H), 4.81 (d, *J* = 15.6 Hz, 1H), 3.89 (s, 3H), 3.88 (s, 3H), 3.70-3.64 (m, 4H), 3.04 (dd, *J* = 16.4, 6.0 Hz, 1H).

Step 3

Prepared analogously to **25** using methyl (S)-2-(6-cyanobenzo[d]oxazol-2-yl)-6-methoxy-5-((5-methoxypyridin-2-yl)methoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxyl ate **32a** (130 mg, 0.26 mmol) to provide (S)-2-(6-cyanobenzo[d]oxazol-2-yl)-6-methoxy-5-((5-methoxypyridin-2-yl)methoxy)-1,2 ,3,4-tetrahydroisoquinoline-3-carboxylic acid (8 mg, 6%).

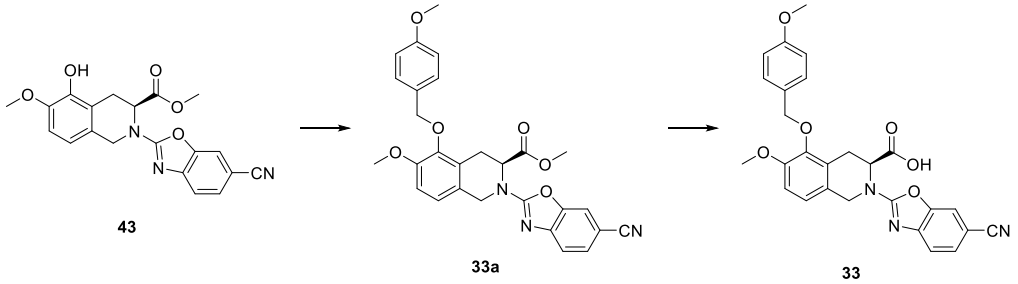
MS *m*/*z* (ESI): calcd for $C_{26}H_{23}N_4O_6$ $[M+H]^+$, 487.2; found, 487.1.

HRMS *m*/*z* (ESI): calcd for $C_{26}H_{23}N_4O_6$ $[M+H]^+$, 487.1618; found, 487.1613.

HPLC: Purity 98.6%.

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.28 (d, *J* = 2.8 Hz, 1H), 8.04 (s, 1H), 7.66 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.55 (d, *J* = 8.8 Hz, 1H), 7.49-7.46 (m, 2H), 7.09 (d, *J* = 8.8 Hz, 1H), 7.02 (d, *J* = 8.4 Hz, 1H), 5.12 (dd, *J* = 6.4, 2.8 Hz, 1H), 4.99 (d, *J* = 11.2 Hz, 1H), 4.91 (d, *J* = 11.2 Hz, 1H), 4.83 (d, *J* = 15.6 Hz, 1H), 4.72 (d, *J* = 15.2 Hz, 1H), 3.85 (s, 3H), 3.83 (s, 3H), 3.55-3.50 (m, 1H), 3.00 (dd, *J* = 17.2, 6.4 Hz, 1H).

(S)-2-(6-Cyanobenzo[d]oxazol-2-yl)-6-methoxy-5-((4-methoxybenzyl)oxy)-1,2,3,4-tet rahydroisoquinoline-3-carboxylic acid (33)



Step 1

Prepared analogously to **32a** using Methyl (S)-2-(6-cyanobenzo[d]oxazol-2-yl)-5-hydroxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate **43** (100 mg, 0.264 mmol) and 4-Methoxybenzylchloride (100 mg, 0.639 mmol) to provide methyl

(S)-2-(6-cyanobenzo[d]oxazol-2-yl)-6-methoxy-5-((4-methoxybenzyl)oxy)-1,2,3,4-tetra-hydroisoquinoline-3-carboxylate (120 mg, 93%).

MS *m*/*z* (ESI): calcd for $C_{28}H_{26}N_3O_6$ $[M+H]^+$, 500.2; found, 500.1.

Chiral HPLC: retension time, 37.23 min, ee = 98.3% (chromatographic column: ChiralPak AD-H, 250 × 4.6 mm, 5 μm; T = 25 ℃; λ = 295 nM; mobile phase: Hexane/^{i}PrOH/TFA = 70/30/0.1 (V/V/V); F = 0.8 mL/min; retension time for enantiomers, 41.18 min, 83.28 min).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (s, 1H), 7.53 (d, *J* = 8.4 Hz, 1H), 7.46 (d, *J* = 7.6 Hz, 1H), 7.37 (d, *J* = 8.4 Hz, 2H), 6.95-6.87 (m, 4H), 5.15 (s, 1H), 5.00 (d, *J* = 10.8 Hz, 1H), 4.93-4.89 (m, 2H), 4.79 (d, *J* = 15.6 Hz, 1H), 3.90 (s, 3H), 3.82 (s, 3H), 3.64- 3.59 (m, 4H), 2.90 (dd, *J* = 16.2, 6.6 Hz, 1H).

Step 2

Prepared analogously to **25** using methyl (S)-2-(6-cyanobenzo[d]oxazol-2-yl)-6-methoxy-5-((4-methoxybenzyl)oxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate **33a** (130 mg, 0.260 mmol) to provide (S)-2-(6-cyanobenzo[d]oxazol-2-yl)-6-methoxy-5-((4-methoxybenzyl)oxy)-1,2,3,4-tetrah ydroisoquinoline-3-carboxylic acid (60 mg, 48%).

MS *m*/*z* (ESI): calcd for $C_{27}H_{24}N_3O_6$ $[M+H]^+$, 486.2; found, 486.1.

HRMS *m*/*z* (ESI): calcd for $C_{27}H_{24}N_3O_6$ $[M+H]^+$, 486.1665; found, 486.1654.

HPLC: Purity 95.8%.

Chiral HPLC: retension time, 21.23 min, ee = 96.4% (chromatographic column: Chiralcel OD-RH, 150 × 4.6 mm, 5 μm; T = 25 ℃; λ = 300 nM; mobile phase: Acetonitril/50 mM KPF6 (adjust pH to 2.0 with H_3PO_4) = 60/40/0.1 (V/V); F = 0.5 mL/min; retension time for enantiomers, 21.23 min, 23.34 min).

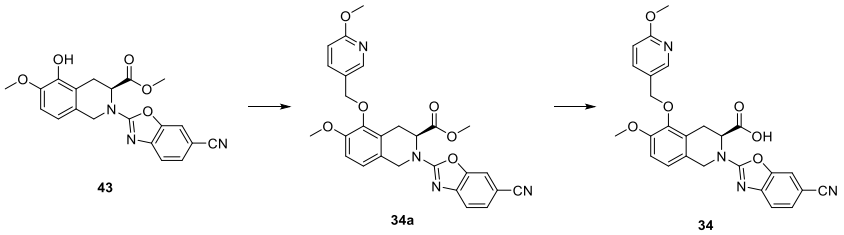
$[\alpha]_D^{20}$ + 25.8 (*c* 1.00, MeOH).

^{1}H NMR (400 MHz, DMSO-d_6) δ 13.12 (s, 1H), 8.04 (s, 1H), 7.67 (d, *J* = 8.0 Hz, 1H), 7.80 (d, *J* = 8.4 Hz, 1H), 7.38 (d, *J* = 8.4 Hz, 2H), 7.07 (d, *J* = 8.4 Hz, 1H), 7.01 (d, *J* = 8.4 Hz, 1H), 6.95 (d, *J* = 8.8 Hz, 2H), 5.11 (dd, *J* = 5.4, 2.2 Hz,1H), 4.91 (d, *J* = 10.0 Hz, 1H), 4.83-4.78 (m, 2H), 4.71 (d, *J* = 15.6 Hz, 1H), 3.84 (s, 3H), 3.76 (s, 3H), 4.52 (dd, *J* = 15.4, 1.8 Hz, 1H), 2.90 (dd, *J* = 16.4, 6.8 Hz, 1H).

^{13}C NMR (100 MHz, DMSO) δ 172.10, 164.21, 159.72, 148.25, 147.95, 146.46, 143.75, 130.81, 130.11, 129.98, 124.50, 119.95, 119.31, 117.00, 116.94, 114.47, 113.24, 111.00, 102.39, 59.70, 56.41, 55.62, 54.60, 45.34, 24.76.

(S)-2-(6-Cyanobenzo[d]oxazol-2-yl)-6-methoxy-5-((6-methoxypyridin-3-yl)methoxy)-

1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (34)



Step 1

Prepared analogously to **32a** using methyl (S)-2-(6-cyanobenzo[d]oxazol-2-yl)-5-hydroxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate **43** (100 mg, 0.264 mmol) and 5-(Chloromethyl)-2-methoxypyridine (100 mg, 0.635 mmol) to provide methyl
(S)-2-(6-cyanobenzo[d]oxazol-2-yl)-6-methoxy-5-((6-methoxypyridin-3-yl)-methoxy)-1, 2,3,4-tetrahydroisoquinoline-3-carboxylate as crude (130 mg). The NMR sample was purified by silica gel chromatography.

MS *m*/*z* (ESI): calcd for $C_{27}H_{25}N_4O_6$ $[M+H]^+$, 501.2; found, 500.9.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (s, 1H), 7.88 (d, *J* = 8.4 Hz, 1H), 7.58 (s, 1H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.44 (d, *J* = 8.0 Hz, 1H), 6.97-6.87 (m, 3H), 5.24 (s, 1H), 5.03 (d, *J* = 10.8 Hz, 1H), 4.97-4.91 (m, 2H), 4.80 (d, *J* = 15.2 Hz, 1H), 4.01 (s, 3H), 3.90 (s, 3H), 3.67-3.61 (m, 4H), 2.96 (dd, *J* = 16.4, 6.0 Hz, 1H).

Step 2

Prepared analogously to **25** using methyl (S)-2-(6-cyanobenzo[d]oxazol-2-yl)-6-methoxy-5-((6-methoxypyridin-3-yl)methoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxyl ate **34a** (130 mg, 0.260 mmol) to provide (S)-2-(6-cyanobenzo[d]oxazol-2-yl)-6-methoxy-5-((6-methoxypyridin-3-yl)methoxy)-1,2,3,4-tetrahydroisoquinoline-3-carboxy-lic acid (55 mg, 44% for two steps).

MS *m*/*z* (ESI): calcd for $C_{26}H_{23}N_4O_6$ $[M+H]^+$, 487.2; found, 486.9.

HRMS *m*/*z* (ESI): calcd for $C_{26}H_{23}N_4O_6$ $[M+H]^+$, 487.1618; found, 487.1616.

HPLC: Purity 98.7%.

$[\alpha]_D^{20}$ + 24.2 (*c* 1.00, MeOH).

^{1}H NMR (400 MHz, DMSO-d_6) δ 13.12 (s, 1H), 8.21 (s, 1H), 8.05 (s, 1H), 7.81 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.67 (d, *J* = 8.4 Hz, 1H), 7.48 (d, *J* = 8.0 Hz, 1H), 7.08 (d, *J* = 8.4 Hz, 1H), 7.01 (d, *J* = 8.4 Hz, 1H), 6.86 (d, *J* = 8.8 Hz, 1H), 5.13 (dd, *J* = 6.0, 2.4 Hz, 1H), 4.95 (d, *J* = 10.8 Hz, 1H), 4.85-4.80 (m, 2H), 4.72 (d, *J* = 16.0 Hz, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 3.50 (dd, *J* = 16.6, 2.2 Hz, 1H), 2.96 (dd, *J* = 16.6, 7.0 Hz, 1H).

^{13}C NMR (100 MHz, DMSO-d_6) δ 171.99, 164.10, 163.99, 151.53, 148.29, 147.98,

147.39, 144.66, 140.33, 130.04, 126.55, 126.28, 124.73, 122.56, 119.94, 117.05, 113.33, 112.09, 110.87, 102.46, 71.78, 56.32, 54.70, 53.68, 45.29, 25.32.

4. In Vitro Assays

AT_2R and AT_1R Competitive Binding Assay.

Typical competition graphics of AT_2R for Angiotesin II, **EMA401** and compound **15** were presented as Figure S2- S4.

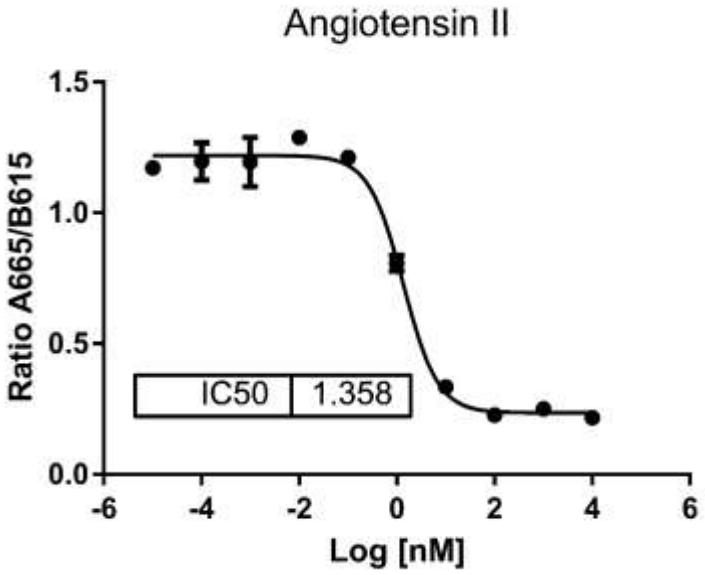


Figure S2. IC_{50} determination curve for Angiotensin II in AT_2R competitive binding assay.

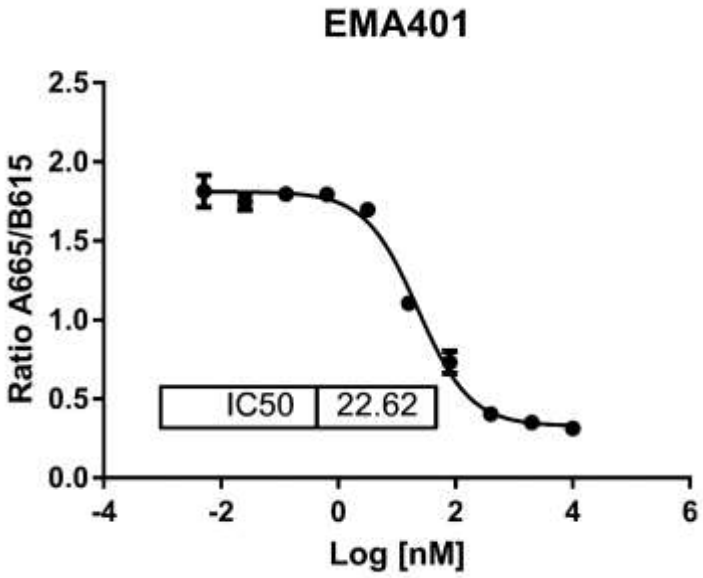


Figure S3. IC_{50} determination curve for **EMA401** in AT_2R competitive binding assay.

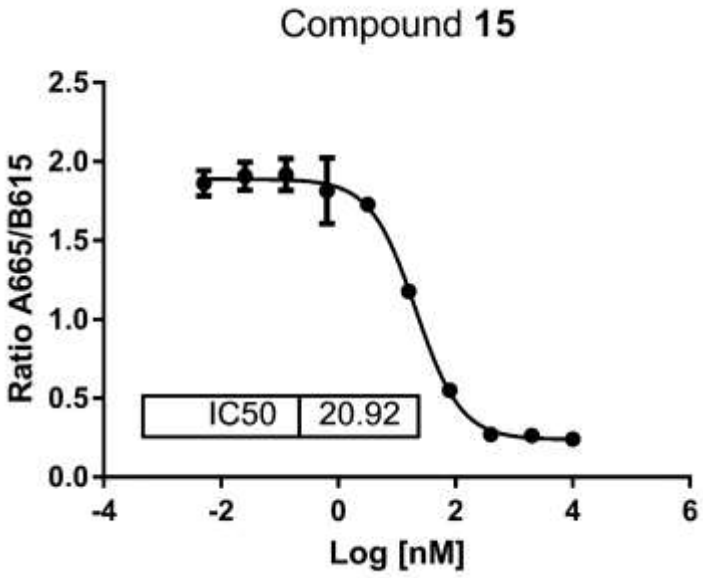


Figure S4. IC_{50} determination curve for compound **15** in AT_2R competitive binding assay.

Typical competition graphics of AT_1R for Angiotesin II, Losartan, **EMA401** and compound **15** were presented as Figure S5- S8.

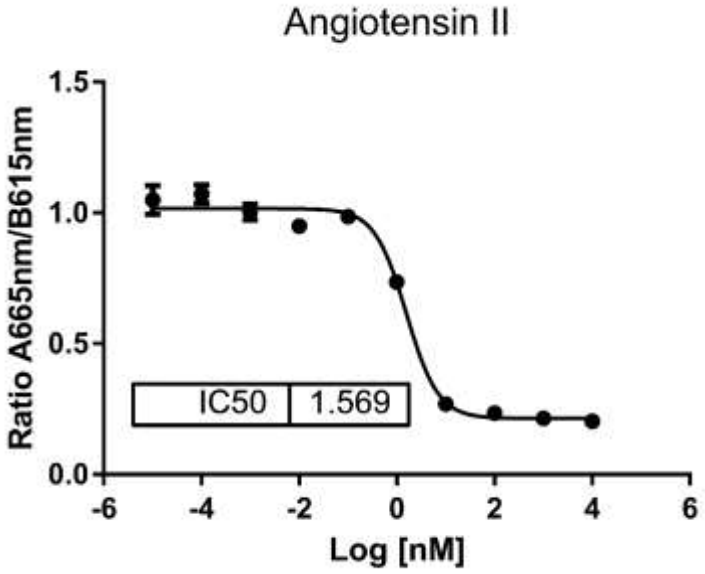


Figure S5. IC_{50} determination curve for Angiotensin II in AT_1R competitive binding assay.

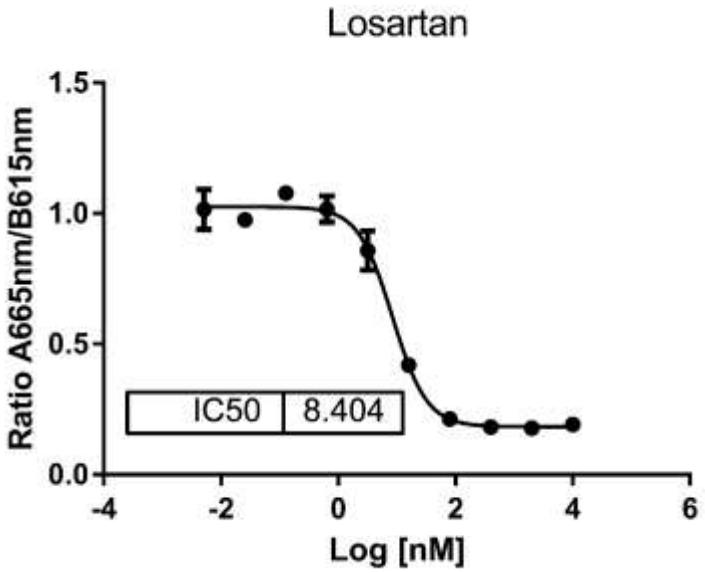


Figure S6. IC_{50} determination curve for Losartan in AT_1R competitive binding assay.

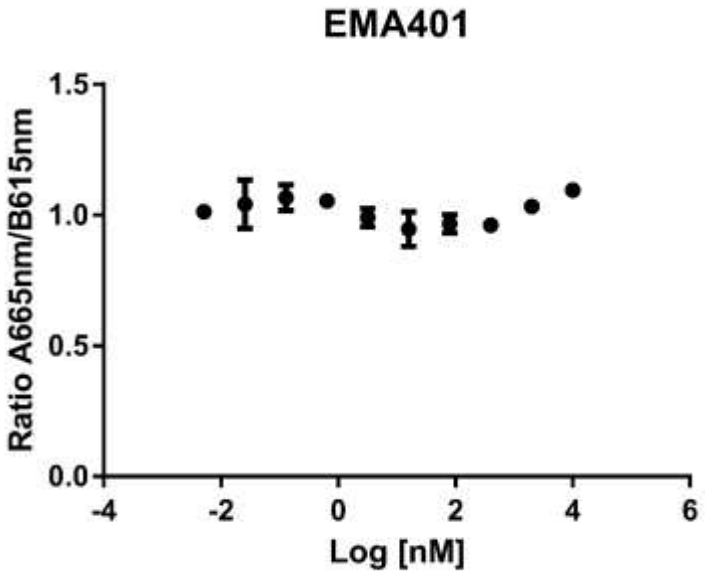


Figure S7. IC_{50} determination curve for **EMA401** in AT_1R competitive binding assay.

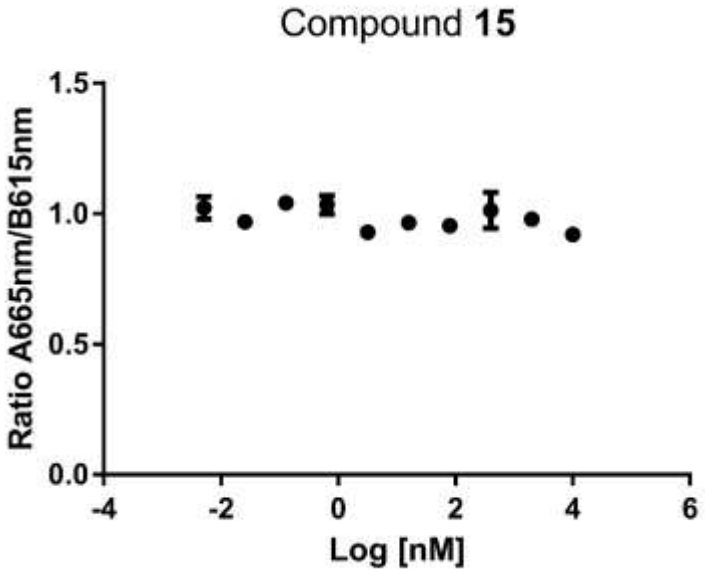


Figure S8. IC_{50} determination curve for compound **15** in AT_1R competitive binding assay.

NG108-15 neurite outgrowth assay

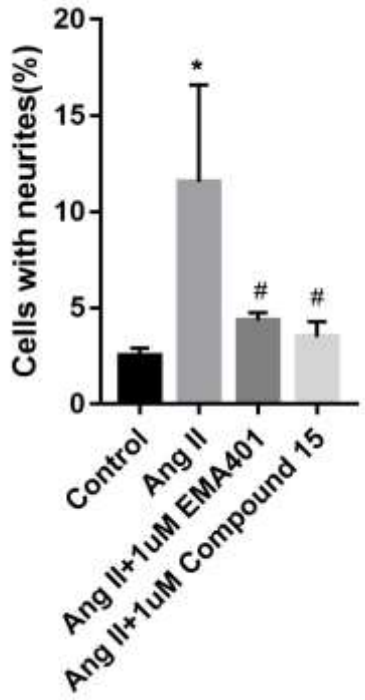


Figure S9. Neurite outgrowth in NG108-15 cells. *, $p<0.05$ Control vs Ang II; #, $p<0.05$ Ang II vs EMA 401 or Compound 15.

Liver Microsome Stability Assay

Liver microsome incubations were performed[4] at 37°C with 1 μM test compound and 0.5 mg/mL microsomes (Corning, catalog number: 452161 or 452501) in 100 mM phosphate buffer solution (pH7.4) with 3 mM $MgCl_2$. Reactions were initiated by addition of NADPH with the final concentration of 1 mM. Final incubation volume was 0.2 mL. 20 μL aliquots were removed from the incubation mixture at 0, 5, 15, 30 and 60 minutes and quenched by 200 μL acetonitrile containing internal standard (Verapamil and Glibenclamide). Denatured proteins were precipitated by centrifugation at 3700 rpm for 10 min, and the supernatants were transferred into a new plate and analyzed by LC-MS/MS. $T_{1/2}$ and CL_{int} were calculated. Results were the geometric mean values of two measurements.

Human Hepatocytes Metabolic Stability Assay

Human hepatocyte stability assay was performed according to previous mentioned methods[5]. Briefly, Cryopreserved hepatocytes (IVT, catalog number: X008000) were thawed, centrifuged and re-suspended to 1.0×10^6 cells/mL in William's E Medium at 37

ºC. 48 μL human hepatocyte were transferred into plate wells with the final concentration of 1 μM test compound. The reactions were performed in 37 °C incubator. At time point of 0, 5, 15, 30, 60 and 90 minutes, the reactions were quenched with 150 μL/well cold acetonitrile containing internal standard (Verapamil and Glibenclamide) and shake at 300 rpm for 10 minutes. Then the plates were centrifuged at 3200g for 20 minutes. The supernatants were aspirated, reconstituted and analyzed by LC/MS/MS. $T_{1/2}$ and CL_{int} were calculated.

CYP Inhibition Assay

Incubations were performed with 0.1 mg/mL human liver microsome (Corning, catalog number: 452161) and a cocktail of six probe substrates[6] (40 μM Phenacetin for CYP1A2, 2 μM Amodiaquine for CYP2C8, 5 μM Diclofenac for CYP2C9, 40 μM S-Mephenytoin for CYP2C19, 5 μM Dextromethorphan for CYP2D6, 2 μM Midazolam for CYP3A4) in 100 mM phosphate buffer solution (pH 7.4) with 3 mM $MgCl_2$. The compounds were tested in 6-dose with a 3-fold serial dilution starting at 50 μM. The reactions were initiated by the addition of NADPH with the final concentration of 1 mM. After 15 minutes incubation, reactions were quenched with cold acetonitrile containing internal standard (Verapamil and Glibenclamide). Denatured proteins were precipitated and centrifuged at 3700 rpm for 10 minutes, and the supernatants were transferred into new plates. The metabolites (acetaminophen, N-Desethyl amodiaquine, 4-hydroxydiclofenac, 4-hydroxymephenytoin, Dextrorphan and 1-hydroxy-Midazolam) were analyzed by LC-MS/MS. A decrease of the metabolites in peak area compared to vehicle control is used to calculate an IC50 value by using Prism 5.0 software (Graphpad).

hERG Patch Clamp Assay

The hERG channel activity were measured by automated QPatch[7] (Sophion, Denmark). A CHO cell line stably transfected with hERG cDNA and expressing hERG channels was used for the study. The external solution contained 2 mM $CaCl_2$, 1 mM $MgCl_2$, 4 mM KCl, 145 mM NaCl, 10 mM glucose and 10 mM HEPES (pH 7.4, adjusted with NaOH). The internal solution contained 5.347 mM $CaCl_2$, 1.75 mM $MgCl_2$, 120 mM KCl, 10 mM HEPES, 5 mM EGTA and 4 mM Na-ATP (7.25, adjusted with KOH). Test compounds were dissolved in DMSO to a stock concentration of 10 mM, then diluted to 1 & 10 μM by external solution. Whole-cell recordings were performed using automated QPatch (Sophion, Denmark). The cells were voltage clamped at a holding potential of -80 mV. The hERG current was activated by depolarizing at +20 mV for 5 sec, after which the current was taken back to -50 mV for 5 sec to remove the inactivation and observe the

outward tail current. The maximum amount of tail current was used to determine hERG current amplitude. After achieving break-in (whole-cell) configuration, the cells were recorded for 120 sec to assess current stability. The voltage protocol described above was then applied to the cells every 15 sec throughout the whole procedure. Only stable cells with recording parameters above threshold were allowed to enter the drug application procedure. All experiments were conducted at room temperature (about 25^{o}C). External solution containing 0.1% DMSO (vehicle) was applied to the cells to establish the baseline. After allowing the current to stabilize for 3 minutes, test compound was applied. Test compound solution was added and the cells were kept in the test solution until the compound's effect reached a steady state or for a maximum of 4 min. Washout with external solution was performed until the recovery of the current reached a steady state. Positive control cisapride is used to test the same batch of cells to ensure the normal behavior and good quality of the hERG cells.

Plasma Protein Binding Assay

The plasma protein binding rate was measured by equilibrium dialysis[8]. The test compound at 1.0 μM concentration were mixed with plasma (3D BioOptima). After incubation, 10 μL plasma sample was transferred into the donor side of 96-well dialysis device (HTDialysis), added with 90 μL phosphate buffer (100 mM, 0.002% Tween-80, pH 7.4) and vortexed. 90 μL phosphate buffer (100 mM, 0.002% Tween-80, pH 7.4) was transferred into the receiver side added with 10 μL blank plasma and vortexed. Then the apparatus was incubated at 37°C for 6 hours. After dialysis, 100 μL Aliquots from donor side and receiver side samples were supplemented with 400 μL of precipitant, vortexed well and centrifuged 10 minutes at 3700 rpm. Then, 70 μL of the supernatant was removed and diluted by 70 μL of water. After vortexed, 10 μL aliquot was analyzed by LC-MS/MS. Results were the geometric mean values of two measurements.

Caco-2 Cell Permeability Assay

The Caco-2 cells (American Tissue Culture Collection) were seeded on polycarbonate cell culture insert plate (Millipore, catalog number: PSHT010R5) and cultured for 21 days prior to the transport experiments[9]. Test compounds were dissolved in DMSO (10 mM) and diluted to a final concentration of 10 μM in HBSS buffer containing 25 mM HEPES, pH 7.4. To evaluate apical to basolateral transport (A to B), 600 μL of A-to-B dosing solution was placed on the apical side with 800 μL 0.4% DMSO HBSS buffer in the basolateral compartment. To evaluate basolateral to apical transport (B to A), 900 μL B-to-A dosing solution was placed on the basolateral side with 500 μL 0.4% DMSO

HBSS in the apical compartment. The assay was initiated by placing the apical plate onto basolateral plate, and incubated at 37 ^{o}C for 90 min. At the end of incubation, analytical samples were prepared (6 μL sample + 54 μL 0.4% DMSO/HBSS + 70 μL acetonitrile with osalmid and imipramine as internal standards for donor, 60 μL sample + 70 μL acetonitrile with osalmid and imipramine as internal standards for receiver) and analyzed by LC-MS/MS. Results were the geometric mean of two measurements.

5. In Vivo Assay

Animals utilized in preclinical studies included Sprague Dawley (SD) rats and beagle dogs. SD rats were purchased from Beijing Vital River Laboratory Animal Technology Co., Ltd, and beagle dogs from Beijing Marshall Biotechnology Co. LTD. All experimental protocols were approved by the Hisun Institutional Animal Care and Use Committee and all animals were treated in accordance with the Guide for the Care and Use of Laboratory Animals.

In Vivo Pharmacokinetic Studies

For p.o. study, Three male Sprague Dawley rats were administrated by oral gavage at a dose of 10 mg/kg test compound as a suspension in 0.5% CMC-Na solution; Three male dogs were administrated by oral gavage at a dose of 3 mg/kg test compound as a suspension in 0.5% CMC-Na + 0.5% Tween 80 solution For i.v. study, Three male Sprague Dawley rats were administrated by intravenous injection at a dose of 1 mg/kg test compound as a solution in DMA: 30% Solutol HS-15: saline (v: v: v = 20: 20: 60); Three male dogs were administrated by intravenous injection at a dose of 1 mg/kg test compound as a solution in DMA: Kolliphor HS 15: saline (v: v: v = 20: 6: 74). Blood samples (0.15 mL for rats and 0.5 mL for dogs) were collected via cephalic vein at times of 0.083, 0.25, 0.5, 1, 2, 4, 8, 12, and 24 h after administration. Plasma was separated by centrifugation at 2000 g, 4 °C for 5 minutes and was kept at -70 °C before analysis by LC/MS/MS.

Blood Brain Barrier Penetration Assay

Three male Sprague Dawley rats were administrated orally with test compound as a suspension in 0.5% CMC-Na and 0.5% Tween-80 solution (3 mg/kg for compound **15** and 30 mg/kg for EMA-401). At 1 hour post-dosing, rats were anesthetized with CO_2. Blood samples (0.5 mL) were collected via cardiac puncture and transferred to EDTA-K_2 anticoagulant tubes. Plasma was separated by centrifugation at 1500 g for 10 min and diluted with acetonitrile containing glibenclamide and verapamil as internal standards.

Brain tissue samples were taken immediately after the blood sample collection and homogenized with 20% methanol solution at a ratio of 1:3 (w/v). The plasma samples and the tissue homogenates were analyzed by LC-MS/MS. Results were the geometric mean of three measurements.

7-Day Acute Rat Toxicity Study

Sprague Dawley rats were randomized to seven groups (n = 8, 4 males and 4 females). The rats were administrated by oral gavage at dosages of 200, 400, and 800 mg/kg daily for 7 days or equal volume of 0.5% CMC-Na and 0.5% Tween 80 in water. During the experiment, the weight and food intake of the rats were measured. The toxic reaction and death of the rats were observed every day, including changes in activities, food intake, poisoning symptoms, hair color, external reaction and feces of the rats. Hematology and blood biochemical parameters were measured on the 8th day.

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